EXHIBIT A

i3 Engineering Sciences
Invent. Innovate. Implement.

Independent Test Report

SUMMARY: i3 Engineering Sciences LLC has completed an independent test project to measure the static sun protection factor (SPF) of **elta MD** skincare sunscreen.

TESTING PERIOD: Testing period September 2015; final report issued 10/16/2015

Table of Contents

Project Summary

BACKGROUND: The sun produces ultraviolet (UV) A and ultraviolet B rays that reach the Earth, which are part of an electromagnetic spectrum. UVA ray wavelengths range from 400 nanometers to 320 nanometers, while UVB rays range from 320 nanometers to 290 nanometers. UVA can penetrate both the upper layer of skin, the epidermis, as well as the lower layer of skin, the dermis. It is most often responsible for damaging keratinocytes in the epidermis, where skin cancer is typically found. UVB, although it does not penetrate the dermis, is more intense because of its shorter wavelengths. However, both can be extremely harmful to humans, as they can cause sunburns, skin cancer, and other skin damage.

In order to prevent these problems from happening, sunscreen use is recommended.
Sunscreen protects skin by either absorbing or reflecting the harmful ultraviolet rays, preventing them from reaching the skin. Sunscreen is tested and rated for its Sun Protection Factor (SPF), which determines the ratio of the UV radiation dose it takes to cause a barely detectable sunburn on a person treated with a sunscreen product and an untreated person. SPF values only reflect protection against the portion of the UV spectrum that causes sunburn – UVB rays, the chief culprit behind sunburn. UVA rays are more associated with wrinkling, leathering, sagging and other light-induced effects of aging. They also exacerbate the carcinogenic effects of UVB rays.

SPF 15 is the FDA's minimum recommendation for protection against skin cancer and sunburn; although industry organizations such as the American Academy of Dermatology, recommend choosing a sunscreen with an SPF of at least 30.

APPROACH: This is a non-randomized in vivo persistent pigment darkening (PPD) study with blinded evaluations; the objective is to measure static SPF of **elta MD** sunscreen according to the 2011 FDA Final Rule [Appendix 1]. SPF is the measure of sunscreen's ability to prevent UVB from damaging the skin; currently there is no internationally accepted standard for testing and measuring UVA protection (Broad Spectrum products are designed to provide protection against both UVA and UVB exposure).

The FDA Final Rule describes the procedures for determining the Static sun protection factor (SPF). The Static SPF is defined by the ratio of the minimal erythema dose of ultraviolet radiation for sunscreen-protected skin to that for unprotected skin. The minimal erythema dose (MED) is the dose of ultraviolet (UV) radiation that produces perceptible redness of the skin with clearly defined borders, 16 to 24 hours after administration. Timed UV radiation doses are administered using a xenon arc lamp that simulates solar radiation.

Subjects included healthy male and/or female volunteers with skin types I, II and/or III for each test product. They are all at least 18 years old, providing legally effective, written informed consent; willing and able to keep study appointments and follow instructions; have good general health; and are willing to avoid sun and tanning lamp exposure during the study.

The application of products for SPF determination on the back between the belt-line and shoulder blades was applied by a technician during each visit; the technician documented UV doses, times completed, lamp effective irradiance readings before and after UV doses to each test product and immediate response codes after each UV dose. The grading scale, zero to 6, for erythema responses to the UV doses administered to untreated sites and sunscreen treated sites meet the FDA requirements.

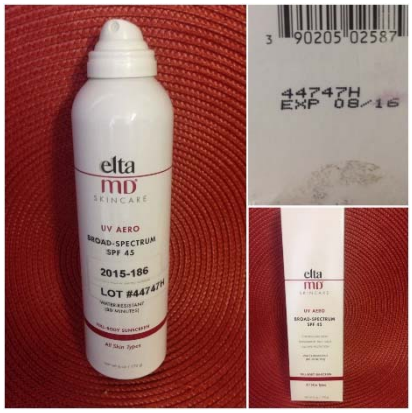
Chain of Custody was maintained throughout the testing as evidenced by Appendix 3.

SPECIFICATIONS: All specifications regarding test subjects, solar simulators, test protocol and measurement standards complied with requirements in the 2011 FDA Final Rule, the most notable of which requires:

- The test panel to produce a minimum of 10 valid test results. A maximum of three subjects may be rejected from the panel. Therefore, if 3 subjects would be rejected, a test panel would have had to include 13 subjects. The FDA "reduced the number of test subjects in this document (the 2011 Final Rule) because the data demonstrates that SPF testing can be conducted with adequate accuracy and precision using as few as 10 test subjects, even when testing high SPF products."
- The test panel volunteers to have a skin type of I, II or III on the Fitzpatrick phototyping scale.
- The testing pattern of products at 2 milligrams per square centimeter of skin.
- The irradiation source will be a solar simulators including a single-port or multi-port xenon arc lamps with UVC blocking filters, visible and infrared blocking filters and heat-rejected dichroic mirrors, used in this testing protocol
- The placement of the test sub-sites and the adherence to dose administration guidelines.
- The use of set computations to determine SPF values for individual subjects, standard deviation, standard error and labeled SPF value.
- The use of the reference standard 7% Padimate- 0.3% Oxybenzone to validate the test protocol and measurement methods.
- Labeling to identify the type of UV protection a sunscreen offers and what a sunscreen can do. The label is required to quantify the SPF factor, and whether the product is Broad Spectrum in a combined statement prominent on the label; state whether the product is Water Resistant (effective for up to 40 minutes in water) or Very Water Resistant (effective for up to 80 minutes in water); and include a Skin Cancer/Skin Aging Alert in the Drug Facts section of the label.

Results

Product: elta MD Spray - Lot # 44747H



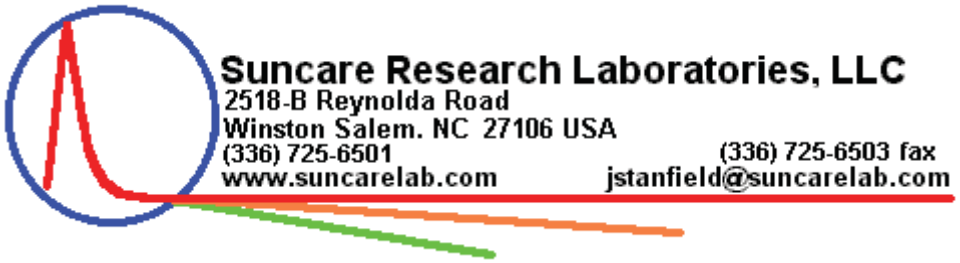
Summary:

The test product had an expected SPF of 45. Two separate panels were run. The mean static SPF of the test product in the first panel was 22.17. A second panel was seated utilizing the same test product to further validate results. The mean static SPF of the test product in the second panel was 19.71. The test product does not meet FDA Final Rule requirements for labeling as Static SPF 45 as listed on its label.

As part of the standard Test Protocol a known standard sunscreen, in this case 7% Padimate- 0.3% Oxybenzone, is tested concurrently with the product under test, as well as unprotected skin. In order for the SPF determination of the test product to be valid, the measured SPF value of the test standard must fall within the standard deviation range of the expected SPF, in this case, + or - 3.43. The measured SPF of the 7% Padimate- 0.3% Oxybenzone standard was within the required range, validating the test product results.

The elta MD spray met the FDA Final Rule requirements for labeling as Static SPF 18.

Lab Reports



Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem. NC 27106 USA
(336) 725-6501 (336) 725-6503 fax
www.suncarelab.com jstanfield@suncarelab.com

SRL2015-186: Evaluation of the Static Sun Protection Factor (SPF) of Sunscreen-Containing Formulas According to the FDA Final Rule [1]

September 28, 2015

Final Report

Objective: To measure the static sun protection factor (SPF) of over-the-counter (OTC) sunscreen-containing formulas according to the FDA Final Rule [1]

Test Product: Elta MD Spray – Lot #44747H

Study Dates: September 9, 2015 to September 23, 2015

Results: Six subjects completed the test. The mean static SPF of the test product, Elta MD Spray – Lot #44747H, was 22.17 (n=4, SD=2.41). Two of the subjects did not yield valid SPF results for the test product. The test product would be likely to meet FDA Final Rule requirements for labeling as Static SPF 22. [1]

Sponsor: i3 Engineering Sciences LLC
P.O. Box 1808
Bluefield, WV 24701

Joanne McFadden, Principal
(304) 918-0670
jjxmcfadden@i3engineeringsciences.com

Investigator: Joseph W. Stanfield, M. S.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

Summary:
On the first day of the study each subject received a series of UV doses from a xenon arc solar simulator to an unprotected site on the mid-back. The solar simulator was a single-port xenon arc lamp with a 1 mm WG320 UVC blocking filter, a 1 mm UG-11 visible and infrared blocking filter and a heat rejecting dichroic mirror (Model 16S, Solar Light Co., Philadelphia). On the second day the minimal erythema dose (MED) was determined as the lowest UV dose which produced perceptible erythema with clearly defined borders. Then 100 mg of the test product and 100 mg of the 7% Padimate-O/3% Oxybenzone standard were applied to separate, adjacent 50 cm^2 areas of the mid-back (standard sunscreen provided by Cosmetech Laboratories, Inc., Fairfield, NJ). Each sunscreen-protected site was divided into five subsite test areas that were at least 0.5 cm^2 in area for UV exposures.

Initially, the test product had an expected SPF of 45 and the expected SPF was lowered based on previous results to between 20-25. The 7% Padimate-O/3% Oxybenzone standard sunscreen had an expected SPF of 16.3. After a 15-minute drying period UV doses ranging from 0.76 to 1.32 times the product of the MED and the expected SPF were administered to the test sunscreen-protected area and UV doses ranging from 0.76 to 1.32 times the product of the MED and 16.3 were administered to the standard sunscreen protected areas. A series of UV doses were also administered to a second unprotected site. On the third day the MED was determined for the sunscreen-protected sites (MEDp) and the unprotected sites (MEDu). The SPF of each sunscreen was calculated as the ratio of the MEDp for each sunscreen-protected site to the Final MEDu. The Final MEDu used for SPF computation was the Repeat MEDu for all of the subjects tested.

Detailed procedures for determining the Static Sun Protection Factor according to the FDA Final Rule [1] are described in the protocol.

Details of calibrations for the Solar Simulators used in this testing are shown in the APPENDIX.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

According to the FDA Final Rule [1], the labeled SPF must be calculated as follows:

SPF values for individual subjects (SPFi) will be calculated as:

$SPFi = MEDp/MEDu$

The mean SPF and standard deviation (SD) will be calculated from valid SPFi values.

The Standard Error (SE) will be calculated as:

$SE = SD/\sqrt{n}$

Where n equals the number of subjects who provided valid test results.

The t value from Student's t distribution table corresponding to the upper 5% point with n-1 degrees of freedom will be obtained.

The labeled SPF value will be determined as the largest whole number less than the following calculation after 10 at least 10 subjects:

$Labeled\ SPF = Mean\ SPF - (t * SE)$

In order for the SPF determination of the test product to be valid, the SPF value of the 7% Padimate-O and 3% Oxybenzone Standard should fall within the standard deviation range of the expected SPF (i.e. 16.3 ± 3.43 or 12.87 to 19.73)

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

Results:
Six subjects, 1 man and 5 women, who provided written, informed consent, completed the study. Subjects included 1 with skin type I, 2 with skin type II and 3 with skin type III.[1] Ages ranged from 30 to 61 years and the mean age was 45.83 (n=6, SD=11.58). Subject demographic and static SPF results are listed in Table 1.

The mean static SPF of the test product, Elta MD Spray – Lot #44747H, was 22.17 (n=4, SD=2.41). Two of the subjects did not yield valid SPF results for the test product.

The mean SPF of the 7% Padimate-O/3% Oxybenzone standard was 17.42 (n=6, SD=1.28) [1].

Protocol Deviations:
There was a lamp malfunction during Day 2 procedures on Subject 06 resulting in test failure on all sunscreen sites. Data for this subject were rejected.

Enrollment:
All of the subjects enrolled in this portion of the study completed all study procedures. Data for Subject 06 were rejected due to equipment malfunction. Two test products were tested using this protocol number and subject numbers may not appear sequentially in presentation of results.

Adverse Events:
No Adverse Events were reported.

Table 1. Subject Demographic and Static SPF Results for Elta MD Spray - Lot #44747H and 7% Padimate/3% Oxybenzone Standard

SRL2015-186: i3 Engineering Sciences LLC
2011 FDA Final Rule Static SPF

									Elta MD Spray - Lot #44747H		7% Padimate-O/3% Oxybenzone Standard	
Tech Initals	Subject #	SRL ID#	Initials	Age	Sex	Skin Type	MED_{uI} (eff J/m^2)	MED_{uR} (eff J/m^2)	$tpMED_p$ (eff J/m^2)	SPF	$ssMED_p$ (eff J/m^2)	SPF
NLK	01	3071	SDR	30	F	I	230.11	224.83	<7870.06	<35.00	3745.00	16.66
BGS/NLK	03	3567	SLP	35	F	II	223.33	223.17	<7631.56	<34.20	4185.00	18.75
AOS	07	3533	PFS	61	F	III	183.33	178.39	4588.00	25.72	3430.33	19.23
NLK	08	2797	CDF	47	F	III	223.78	227.00	4873.50	21.47	3644.89	16.06
NLK/BGS	14	3173	JAH	54	M	II	200.22	196.44	4002.00	20.37	3262.44	16.61
NLK/BGS	15	3151	PLB	48	F	III	122.83	116.50	2459.33	21.11	2006.00	17.22
			Mean=	45.83					Mean=	22.17		17.42
			SD=	11.58					SD=	2.41		1.28
			n=	6					n=	4		6

Subject 06 - Data Rejected - Lamp malfunction requiring lamp changes likely leading to test failures

Table 1. Subject Demographic and Static SPF Results for Elta MD Spray - Lot #44747H and 7% Padimate/3% Oxybenzone Standard

SRL2015-229: i3 Engineering Sciences LLC
2011 FDA Final Rule Static SPF

									Elta MD Spray - Lot #44747H		7% Padimate-O/3% Oxybenzone Standard	
Tech Initals	Subject #	SRL ID#	Initials	Age	Sex	Skin Type	MED_{ul} (eff J/m^2)	MED_{uR} (eff J/m^2)	$tpMED_p$ (eff J/m^2)	SPF	$ssMED_p$ (eff J/m^2)	SPF
AOS	01	2535	FAC	45	F	II	225.17	280.00	6541.67	23.36	4219.44	15.07
NLK/AOS	02	2459	JTP	38	M	II	187.00	180.67	4109.72	22.75	3506.67	19.41
AOS	03	3453	CBA	49	M	III	233.44	232.33	<3899.11	<16.78	3801.06	16.36
NLK	04	2839	TEM	54	F	II	146.61	148.06	3228.22	21.80	2389.67	16.14
AOS/NLK	05	2139	EPH	40	M	III	227.33	233.28	<3808.00	<16.32	3705.00	15.88
NLK	06	3235	DGE	57	F	I	148.56	146.61	<2482.00	<16.93	2425.83	16.55
NLK	07	2007	EMM	76	F	III	286.00	291.33	5927.78	20.35	4669.33	16.03
JL	08	1174	SMK	62	F	II	185.89	181.22	3844.50	21.21	3028.67	16.71
JMW	09	3260	MNM	25	F	III	223.83	285.83	4636.00	16.22	4199.00	14.69
JMW/NLK	10	1417	GSL	53	M	II	233.83	235.56	4212.22	17.88	3816.33	16.20
JL	11	3051	AKD	32	M	III	221.00	218.67	3981.78	18.21	3596.00	16.45
NLK	12	3599	RDR	18	F	I	144.22	146.22	2596.67	17.76	2350.00	16.07
JMW/NLK	13	3247	LDV	24	F	II	147.00	150.67	2651.22	17.60	2750.33	18.25
			Mean=	44.08					Mean=	19.71		16.45
			SD=	16.73					SD=	2.49		1.22
			n=	13					n=	10		13
									SE=	0.79		0.34
									t=	1.83		1.78
									Labeled SPF =	18		15
											Mean: Valid (Y/N)	Yes
											Labeled: Valid (Y/N)	Yes

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

Conclusion:

The test product, Elta MD Spray – Lot #44747H, would be likely to meet the FDA Final Rule requirements for labeling as Static SPF 22. [1]

Joseph W. Stanfield, M. S. – Investigator

28-Sep-2015
Date

References:

1. U. S. Food and Drug Administration. Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use; Final Rule; 21 CFR Parts 201 and 310. Federal Register, Vol. 76, No. 117, June 17, 2011. pp. 35660-35665.
2. Guideline for the colorimetric determination of skin color typing and prediction of the minimal erythema dose (MED) without UV exposure. Colipa, 2007.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

APPENDIX

LAMP CALIBRATIONS

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501 (336) 725-6503 (Fax)
www.suncarelab.com

Calibration of Lamps for SPF Testing

25-Aug-2015

Calibration of Lamps 10, 14, 19, 20, 23 (Calibration Due)

Range (nm)	Lamp 10 S/N 9655 Bulb 338881 (10-Feb-16)	Lamp 14 S/N 11476 Bulb 34035 (24-Feb-16)	Lamp 19 S/N 13837 Bulb 340340 (06-Dec-15)	Lamp 20 S/N 5706 Bulb 338032 (30-Aug-16)	Lamp 23 S/N 5706 Bulb 338030 (29-Sep-15)	FDA2011 [1] Colipa 2006 [2] ISO24444 [3] RCEE %
<290	0.04%	0.08%	0.05%	0.02%	0.0%	<0.1
290-300	5.0%	3.0%	4.8%	4.2%	5.0%	1.0-8.0
290-310	56.7%	51.9%	56.7%	54.7%	57.7%	49.0-65.0
290-320	86.5%	85.6%	87.3%	85.8%	87.3%	85.0-90.0
290-330	92.2%	92.2%	93.1%	91.8%	93.0%	91.5-95.5
290-340	94.6%	94.8%	95.3%	94.3%	95.2%	94.0-97.0
290-400	100.0%	99.9%	100.0%	100.0%	100%	99.9-100
UVAII/UV*	0.24	0.26	0.26	0.26	0.25	>0.20
UVAI/UV*	0.67	0.64	0.64	0.68	0.66	>0.60-
Total Power (W/m^2)	1440	1046	1387	930	894	<1500

Lamps were calibrated using an Optronic Laboratories model OL754 or OL756 spectroradiometer and total power was measured using calibrated Solar meter and an International Light Technologies SED624 #616 thermopile (Calibration certificates attached). All lamps comply with the Final Rule of June 17, 2011 [1] , the International SPF Test Method of 2006 [2], and ISO24444 [3]

Joseph W. Stanfield, President — 25-Aug-2015 Date

References

1. U. S. Food and Drug Administration. Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use; Final Rule; 21 CFR Parts 201 and 310. Federal Register, Vol. 76, No. 117, June 17, 2011. pp. 35660-35665.
2. Cosmetic, Toiletries and Fragrances Association of South Africa, Cosmetics, Toiletries and Fragrances Association (CTFA-US), European Cosmetic, Toiletry and Perfumery Association (COLIPA), Japan Cosmetics Industry Association (JCIA), International Sun Protection Factor (SPF) Test Method, May 2006.
3. ISO 24444, Cosmetics – Sun Protection Test Methods – In Vivo Determination of SPF (Sun Protection Factor), First Edition, 2010-11-15.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501 (336) 725-6503 (Fax)
www.suncarelab.com

Calibration of OL754 Spectroradiometer

3-Jan-2015

Optronic Laboratories Spectroradiometer Model OL754 (Optics Head S/N 99203096) was calibrated inhouse on January 3, 2015, using an OL752-10E Spectral Irradiance Standard (S/N 05102222) and OL65A Programmable DC Current Source (S/N 05213354) that were calibrated at Optronic Laboratories, Orlando, FL, on December 19, 2014.

Joseph W. Stanfield, President, 03-Jan-2015 Date

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501 (336) 725-6503 (Fax)
www.suncarelab.com

Calibration of OL756 Spectroradiometer

14-Apr-2015

Optronic Laboratories Spectroradiometer Model OL756 (S/N 08004054) was calibrated inhouse using an OL752-10E Spectral Irradiance Standard (S/N 05102222) and OL65A Programmable DC Current Source (S/N 05213354) that were calibrated at Optronic Laboratories, Orlando, FL, on 19-Dec-2014. The calibration was performed with the 32 mm aperture of the 6 inch Integrating Sphere (S/N 08100389). The new calibration half bandwidth (HBW) was 0.8 nm. The calibration interval is one year or less.

14-Apr-2015

Joseph W. Stanfield, President, Date

InternationalLight TECHNOLOGIES

CALIBRATION CERTIFICATE

OPTICAL CALIBRATION CERTIFICATE

International Light Technologies certifies that the calibration results published in this certificate were obtained using equipment capable of producing results that are traceable to NIST and through NIST to the International System of Units (SI). ILT is Accredited to ISO/IEC 17025:2005. Calibration conforms to ANSI/NCSI Z540.1-1994 and ANSI/NCSI Z540.3-2006.

Rendered-to: SUNCARE RESEARCH LAB

Detector: SED624 #616 Input Optic: K9 #718

Filter: N/A # Misc.: N/A #

Calibrated With: IL1700 #5134 +5V Bias Off

(PIR) PEAK IRRADIANCE RESPONSE SENSITIVITY FACTOR AS CALIBRATED ON: 24-Jun-2015

1.013E-3 (A)(cm2)(W-1) assuming monochromatic irradiance at 800nm

-0.39% *Change In Sensitivity From Previous Calibration Dated: 18-Aug-2014

Tolerance As Found: ☑ In ☐ Out Tolerance As Left: ☑ In ☐ Out

Unit will read directly in watts per square centimeter when used with an IL1700

REFERENCE PLANE Groove ONE formed by filter or diffuser elements and next element, counted from front surface of assembly.

*difference includes intrinsic detector change, NIST recertification updates, lab experimental error or modifications to the hardware adjustments.

PRIMARY STANDARD: U.S. National Institute of Standards and Technology Detector Response
I219 - November 2005 - NIST Test No. 844/272521-05

INTERNATIONAL LIGHT TECHNOLOGIES PRIMARY TRANSFER STANDARDS:

IL #04/TBLU IL #04/TFRD IL #04/Y

ILT Transfer Uncertainty to Customer = +/- 3% plus NIST Uncertainty of: +/- 0.31%

LIGHT SOURCE: 1P 1000W QTH LAMP OUTPUT: 5.30E-3 W/cm2

INSTRUMENTATION: #6400 @800nm PROCEDURE: OP-0029

TEMPERATURE: 22.8 degrees C HUMIDITY: 45%

CALIBRATED BY:

Calibration Technician: Cathy Olson

Calibration Date: 6/24/2015 Certificate No: 506245905 Sales Order #: 150006

ilac-MRA PJLA Calibration Accreditation# 06765

International Light Technologies, Inc.
10 Technology Drive, Peabody, MA 01960 USA
978-818-6180 / 978-818-6181 *fax*
intl-lighttech.com

InternationalLight TECHNOLOGIES

CALIBRATION CERTIFICATE

ELECTRICAL INSTRUMENTATION CALIBRATION REPORT

This document states that the instrument described below meets or exceeds all manufacturer specifications. The calibration results published in this certificate were obtained using equipment capable of producing results that are traceable to NIST and through NIST to the International System of Units (SI). ILT is Accredited to ISO 17025:2005. Calibration conforms to ANSI/NCSI Z540.1-1994 and ANSI/NCSI Z540.3-2006.

Date: 24-Jun-15 Certificate #: 1506241404E SO#: 150006

Temp: 22 Degrees C Humidity: 48 % Procedure: TP-0113:08NOV2011

Rendered To: Suncare Research Lab

InstrumentModel-S/N: ILT1700 #IL17005134

Calibration/Repair Remarks: None

Parts (If Needed): None

As Found Tolerance In	As Found Tolerance Out	As Found Readings	As Found Permissible Error	Applied Current	Adjusted Readings	Permissible Adjustment Error	As Left Tolerance In	As Left Tolerance Out
☑	☐	9.99E-4	+/- 0.5%	1.000E-3	1.000E-3	+/- 0.2%	☑	☐
☑	☐	1.000E-4	+/-0.5%	1.000E-4	1.001E-4	+/- 0.2%	☑	☐
☑	☐	9.98E-6	+/-0.7%	1.000E-5	9.99E-6	+/- 0.2%	☑	☐
☑	☐	1.000E-6	+/-1.0%	1.000E-6	1.000E-6	+/- 0.2%	☑	☐
☑	☐	9.99E-8	+/-1.0%	1.000E-7	9.99E-8	+/- 0.5%	☑	☐
☑	☐	1.002E-8	+/-1.0%	1.000E-8	1.002E-8	+/- 0.5%	☑	☐
☑	☐	1.004E-9	+/-1.0%	1.000E-9	1.004E-9	+/- 0.5%	☑	☐
☑	☐	1.005E-10	+/-1.5%	1.000E-10	1.002E-10	+/- 1.0%	☑	☐

Tolerance after repair and/or calibration: ☑ In ☐ Out

Measurement Uncertainty: 1mA=±0.065%, 100uA=±0.062%, 10uA=±0.062%, 1uA=±0.065%, 100nA=±0.073%, 10nA=±0.079%, 1nA=±0.084%, 100pA=0.26%

The above Instrument was compared to the Keithley Current Calibrator/Source Model 263 S/N 0730631 calibrated on 3/5/2015 which is traceable to NIST. Calibration Due: 3/5/2016

Calibrated By: Brian Lankshear

Electrical Calibration Tech. Brian Lankshear

International Light Technologies, Inc.
10 Technology Drive, Peabody, MA 01960 USA
978-818-6180 / 978-818-6181 *fax*
intl-lighttech.com

Appendix

1. U.S. Food and Drug Administration. Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use; Final Rule, 21 CFR Parts 201 and 310. Federal Register, Vol. 76, No. 117, June 17, 2011. pp. 35660-35665.

2. Testing Protocol, SRL 2015-186: Evaluation of the Static Sun Protection Factor (SPF) of Sunscreen-Containing Formulas According to the FDA Final Rule. September 3, 2015. Suncare Research Laboratories.

3. Chain of Custody Documentation, i3 Engineering Sciences LLC internal report.

FEDERAL REGISTER

Vol. 76 Friday,
No. 117 June 17, 2011

Part IV

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 201, 310, and 352
Sunscreen Drug Products for Over-the-Counter Human Use; Final Rules and Proposed Rules

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 310

[Docket No. FDA–1978–N–0018] (Formerly Docket No. 1978N–0038)

RIN 0910–AF43

Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing this document to address labeling and effectiveness testing for certain over-the counter (OTC) sunscreen products containing specified active ingredients and marketed without approved applications. This document addresses labeling and effectiveness testing issues raised by the nearly 2,900 submissions that we received in response to the sunscreen proposed rule of August 27, 2007 (2007 proposed rule). The document also identifies specific claims that render a product that is subject to this rule misbranded or would not be allowed on any OTC sunscreen product marketed without an approved application. The document does not address issues related to sunscreen active ingredients or certain other issues regarding the GRASE determination for sunscreen products. The document requires OTC sunscreen products to comply with the content and format requirements for OTC drug labeling contained in the 1999 Drug Facts final rule (published in the **Federal Register** of March 17, 1999, by lifting the delay of implementation date for that rule that we published on September 3, 2004).

DATES: *Effective Date:* This final rule is effective June 18, 2012. For additional information concerning this effective date, see section X in the preamble of this document. The incorporation by reference of a certain publication listed in this rule is approved by the Director of the Federal Register as of June 18, 2012.

Compliance Date: The compliance date for all products subject to this final rule with annual sales less than $25,000 is June 17, 2013. The compliance date for all other products subject to this final rule is June 18, 2012.

Implementation date: FDA is lifting the delay of implementation date for § 201.66 as published at 69 FR 53801, September 3, 2004.

FOR FURTHER INFORMATION CONTACT: Reynold Tan, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5411, Silver Spring, MD 20993, 301–796–2090.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Overview of Document

A. Rulemaking History

This section of the document does not discuss every regulatory action associated with OTC sunscreen products. It highlights the major regulatory actions that are related to the regulatory actions being taken in this document. For a complete list of all regulatory actions associated with OTC sunscreen products, please refer to our Web site: *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm072134.htm.*

In the **Federal Register** of May 12, 1993 (58 FR 28194), we published a proposed rule for OTC sunscreen products that identified active ingredients we tentatively considered to be generally recognized as safe and effective (GRASE), as well as associated labeling and sun protection factor (SPF) testing to be required for these OTC sunscreen products (the 1993 proposed rule). The SPF test and corresponding labeling reflect the level of protection against sunburn, which is caused primarily by UVB radiation. The 1993 proposed rule also explained the importance of protection against UVA radiation (58 FR 28194 at 28232 and 28233). The proposed rule referenced published UVA test methods but did not propose a specific method (58 FR 28194 at 28248 to 28250). Rather, the proposed rule stated that a sunscreen product could be labeled as ''broad spectrum,'' or labeled with a similar statement, if it protected against UVA radiation as demonstrated by one of the published UVA tests or a similar test.

In April 1994, we reopened the administrative record to allow additional submissions concerning UVA-related issues. We also announced a public meeting to be held in May 1994 to discuss UVA testing procedures (59 FR 16042, April 5, 1994). We held the public meeting to gather more information to help us determine the most appropriate UVA test method and labeling.

In November 1997, Congress enacted the Food and Drug Administration Modernization Act of 1997 (FDAMA), which addressed OTC sunscreen products among other FDA issues. Section 129 of FDAMA stated that ''not later than 18 months after the date of enactment of this Act, the Secretary of Health and Human Services shall issue regulations for over-the-counter sunscreen products for the prevention or treatment of sunburn.'' We then determined that the GRASE active ingredients, SPF testing requirements, and related labeling were issues that we could finalize within the timeframe set by FDAMA. Because we had not previously proposed specific UVA testing and labeling requirements, we did not have sufficient time to finalize these UVA requirements within the FDAMA timeframe.

In the **Federal Register** of May 21, 1999, we published a final rule for OTC

sunscreen products (64 FR 27666). The 1999 sunscreen final rule added the sunscreen monograph (regulations) in part 352 (21 CFR part 352) and included an effective date of May 2001. The 1999 sunscreen final rule stated that we would publish a proposed rule outlining UVA testing and labeling requirements at a future date. In 2000, we extended the effective date for the 1999 sunscreen final rule to December 2002 (65 FR 36319, June 8, 2000).

In December 2001, we stayed the December 2002 effective date of the 1999 sunscreen final rule indefinitely. We took this action because we planned to revise part 352 to add UVA testing and labeling requirements so that OTC sunscreen products would be tested and labeled for both UVB and UVA radiation protection. We included these revisions in a proposed rule that published in the **Federal Register** of August 27, 2007 (72 FR 49070). The 2007 proposed rule identified UVA testing and labeling that we proposed should be required for all OTC sunscreen products. The proposed rule also revised SPF testing and corresponding labeling from the 1999 final rule. The proposed rule did not lift the existing stay of the effective date for part 352.

On September 3, 2004 (69 FR 53801), we delayed until further notice the implementation date for the Drug Facts final rule (64 FR 13254, March 17, 1999) (21 CFR 201.66) for OTC sunscreen products. The Drug Facts final rule (21 CFR 201.66) establishes general labeling format and content requirements for all OTC drugs. We explained that we postponed the implementation date for general Drug Facts labeling requirements for sunscreens because we did not expect to issue the sunscreen final rule containing UVA testing and product-specific labeling requirements (*i.e.,* this document) by the Drug Facts implementation date of May 2005. Therefore, we delayed the implementation date until further notice to prevent sunscreen product manufacturers from having to relabel their products at two closely related time intervals, as initially required by the 1999 Drug Facts final rule and the 1999 sunscreen final rule.

B. Scope of This Document

This final rule establishes the labeling and testing requirements for OTC sunscreen products containing specific ingredients or combinations of ingredients and marketed without an approved application under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) (the FD&C Act). The requirements in this final rule will help ensure that these currently marketed sunscreen products are appropriately labeled and tested for both UVA and UVB protection. In addition, the requirements in this final rule will help ensure the proper use of these sunscreens and greater consumer protection from the damaging effects of UV radiation. This final rule also identifies claims that render a product that is subject to this rule misbranded or are not allowed on any OTC sunscreen drug product marketed without an approved application.

As described in the previous section of this document, we issued the 2007 proposed rule as a proposed amendment to the sunscreen monograph requirements in 21 CFR part 352 primarily to establish UVA testing and labeling requirements so that all OTC sunscreen products marketed under the sunscreen monograph would be tested and labeled for both UVB and UVA radiation protection. Sunscreen active ingredients, UVB testing, UVB labeling, and other conditions under which sunscreens would be considered GRASE and not misbranded had been addressed in the 1999 (stayed) final rule. In response to the 2007 proposed rule, however, we received submissions from the public concerning all aspects of the sunscreen monograph (*i.e.,* the conditions specified in the 1999 final rule and the 2007 proposed rule). As discussed further in this section, some of the issues regarding the monograph conditions raised in the public submissions will require further evaluation by us. Therefore, we are not issuing a final monograph with GRASE conditions for sunscreens in this document. Instead, we are publishing this final rule establishing labeling and the effectiveness testing upon which it relies, which applies to the same sunscreens that were the subject of the 2007 proposed rule to amend the monograph, because it is in the best interest of public health to publish this final rule while we work on remaining issues that need to be addressed in order to publish a final monograph. This labeling will help ensure that these products are not misbranded by providing specific indications, directions, warnings, and other important information to help consumers select and use them appropriately.

In this final rule, then, we are codifying in 21 CFR part 201 requirements for OTC sunscreen products containing specified active ingredients and marketed without approved applications under section 505 of the FD&C Act (21 U.S.C. 355) (hereafter referred to as ''covered'' products). With respect to these covered products, this new section 21 CFR 201.327 includes requirements for labeling and the effectiveness testing upon which it relies. Because we have not yet resolved all of the issues regarding conditions under which sunscreens are GRASE and not misbranded, the stay of 21 CFR part 352 remains in effect. Although we are not yet codifying these labeling and related effectiveness testing provisions in the monograph regulation, they do embody the agency's current determination on appropriate regulation of these aspects of sunscreens that were previously identified as falling within the monograph in part 352, and supersede the prior approach embodied in the never-effective provisions of 21 CFR part 352 subparts C and D. While this rule does not lift the stay of part 352, we are lifting the delay of implementation date for the Drug Facts labeling requirements of 21 CFR 201.66. In addition, this rule codifies certain specific claims that render a covered product misbranded or are not allowed on any OTC sunscreen drug product marketed in the United States without an approved application.

We note that all provisions of new 21 CFR 201.327 and the amendments to 310.545 included in this rule apply only to the aforementioned covered products, and references in this document to ''covered'' products recognize this limitation. Manufacturers of sunscreen products that are already being marketed pursuant to an approved application can contact FDA's Center for Drug Evaluation and Research to discuss supplemental submissions that would enable them to include labeling on their products like that specified in this final rule.

C. Issues Outside the Scope of This Document

There are a number of issues that were raised in public submissions responding to the 2007 proposed rule that are outside the scope of this document. The issues fall into two categories:

- GRASE determination for sunscreen products and active ingredients
- Issues affecting multiple OTC drug monographs

As explained below, in this document, we are not addressing these issues related to determining the GRASE status of sunscreen products or sunscreen active ingredients and are not addressing the issues described below affecting multiple OTC drug monographs.

1. Issues Regarding GRASE Determination for Sunscreen Products and Active Ingredients

A large number of submissions on the 2007 proposed rule raised issues related to the conditions that define what constitutes a GRASE finished OTC sunscreen product, irrespective of its active ingredients. These included over 1000 submissions requesting that we limit the monograph to sunscreens that offer broad spectrum protection and have SPF values of 15 or higher. Because this final rule is a labeling rule, and not a monograph, we do not address these issues here but plan to address them in future rulemakings regarding the monograph and conditions for general recognition of safety and effectiveness.

This rule also does not address issues related to the GRASE status of sunscreen active ingredients that are included in the 2007 proposed rule (proposed 21 CFR 352.10 and 352.20). We received 20 submissions raising questions about the safety of ingredients in sunscreens (Ref. 1). Ten of the submissions specifically asked that we ensure that none of the ingredients are carcinogenic. Others asked that we ensure that all ingredients in sunscreens are safe without citing a specific concern. We intend to address carcinogenicity and other safety considerations related to sunscreen active ingredients in a future rulemaking.

We also received submissions requesting that we increase the GRASE concentration of avobenzone from 3 percent to 5 percent (Ref. 1). Another submission points out that there are two USP [1] monographs for zinc oxide:

- Zinc oxide (Ref. 2)
- Zinc oxide neutral (Ref. 3)

The submission would like us to clarify that zinc oxide in OTC sunscreen products can meet the specifications of either USP monograph (Ref. 1). We intend to address all of these issues regarding GRASE determination for sunscreen active ingredients in future rulemakings.

In addition, we received two submissions requesting that we classify three new ingredients not previously marketed in the United States as GRASE: bemotrizinol, bisoctrizole, and octyl triazone (Ref. 1). We found these active ingredients eligible for review under the OTC drug monograph system in 2003 (octyl triazone) and 2005 (bemotrizinol and bisoctrizole) (68 FR 41386, July 11, 2003, and 70 FR 72449, December 5, 2005). We are currently reviewing the safety and effectiveness data submitted for these and other sunscreen active ingredients found eligible for potential addition to the monograph. When we complete our review, we will issue proposed rules stating our tentative conclusions on the safety and effectiveness of all of these ingredients.

2. Issues Affecting Multiple OTC Drug Monographs

This final rule also does not address three issues raised in response to the 2007 sunscreen proposed rule that are not specific to sunscreen products. Because these issues apply more generally to multiple categories of OTC drug products, we are not addressing these issues in this final rule, which is limited to OTC sunscreen products.

The first issue concerns the inclusion of expiration dates on sunscreen labels. We received 12 submissions requesting that we require OTC sunscreen products to be labeled with an expiration date (Ref. 1). Currently, regulations in 21 CFR 211.137(h) do not require that an expiration date be included in labeling if an OTC drug product does not have any dosage limitations and is stable for at least 3 years. This regulation applies to many OTC drug products, including sunscreen products. Any modification of the existing regulations would require publication of a proposed rule addressing all OTC drug products affected by the expiration date regulations.

The second issue concerns the term ''final monograph.'' One submission argued that we should not use this term because it is inaccurate (Ref. 1). As the submission states, ''FDA is to continually evaluate products, so nothing is ever finalized.'' This issue applies to monographs representing all categories of OTC drug products. Therefore, we are not addressing the issue in this document.

The third issue concerns the country of origin listing for all ingredients (*i.e.,* both active and inactive ingredients) on a sunscreen drug product. We received a submission requesting that we provide the country of origin for each ingredient. The submission also requested that manufacturers be required to provide specific details about what each ingredient does in the product. This issue applies to all OTC drug products and, therefore, we are not addressing it in this document.

D. Enforcement Policy

As noted, no final monograph is currently in effect for OTC sunscreen drug products, and in its absence, questions may arise regarding FDA's enforcement policy for OTC sunscreen products marketed without approved applications. To clarify expectations for industry, elsewhere in this issue of the **Federal Register**, we are announcing the availability of a draft guidance document, explaining the agency's intended enforcement policy for these products until a final sunscreen monograph becomes effective.

E. Summary of Major Revisions to the Labeling and Effectiveness Testing Included in the 2007 Proposed Rule

In response to the 2007 proposed rule, we received almost 2,900 submissions from the public. Of these submissions, over 2,500 expressed general support for the proposed rule and urged us to finalize and implement the new rule quickly. Three hundred twenty-five of the submissions raised approximately 90 specific issues related to the proposed rule. We have addressed the issues specifically relating to labeling and effectiveness testing in this final rule. Based on the submissions received, and the information and data included in those submissions or otherwise available to us, we have re-evaluated our position on several issues in the 2007 proposed rule and made several changes to our proposed labeling and testing requirements. Tables 1, 2, 4, and 5 in this document summarize the labeling and effectiveness testing requirements included in the 2007 proposed rule as well as the labeling and effectiveness testing required by this final rule:

- Table 1: PDP Labeling (discussed in section III)
- Table 2: Drug Facts Labeling (discussed in section IV)
- Table 4: SPF Test (discussed in section VI)
- Table 5: Broad Spectrum Test (discussed in section VIII)

Rather than summarizing all of the revisions to the labeling and testing included in the 2007 proposed rule, we are highlighting what we consider to be the most important revisions in this section of the document.

We made the following changes to the proposed labeling:

1. The proposed UVA ''star rating'' is not required on the PDP.

2. A combined ''Broad Spectrum SPF'' statement is required on the PDP for sunscreen products that pass the broad spectrum test established in new 21 CFR 201.327(j). To pass the broad spectrum test, the amount of UVA protection must increase as the SPF value increases.

3. For sunscreen products that pass the broad spectrum test established in new 21 CFR 201.327(j) and have SPF

[1] United States Pharmacopeia.

values of 15 or higher in accordance with the SPF test in 21 CFR 201.327(i):

a. The ''Sun Alert'' warning proposed as the first warning in 2007 is not required (Warning proposed located in 21 CFR 352.52(c)(1)).

b. A new indication statement may be included to inform consumers that using the product ''as directed with other sun protection measures (see Directions [in bold italic font]) decreases the risk of skin cancer and early skin aging caused by the sun.''

c. A new direction statement has been added informing consumers that exposure to the sun increases the risk of skin cancer and early skin aging and providing a list of specific sun protection measures that can decrease this risk.

4. For any OTC sunscreen product that does not pass the broad spectrum test in 21 CFR 201.327(j), or that are broad spectrum with an SPF value less than 15, this final rule, like the 2007 proposed rule, requires that the first warning indicate the adverse consequences of spending time in the sun. The wording of this warning has been revised to state, ''Skin Cancer/Skin Aging Alert [in bold font]: Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, not [in bold font] skin cancer or early skin aging.''

We also made the following changes to the effectiveness testing proposed in 2007:

1. The number of subjects required in the SPF test has been reduced from 20 subjects to 10 subjects.

2. One in vitro test is required to demonstrate broad spectrum protection rather than the two previously proposed tests (an in vitro test and an in vivo test).

3. The broad spectrum test is a pass/fail test based on the critical wavelength value of 370 nm [2].

II. Administrative and Other Issues

Some of the submissions that we received following publication of the 2007 proposed rule made the following requests involving administrative issues (Ref. 1):

- Extend the comment period of the 2007 proposed rule.
- Lift the stay on 21 CFR part 352, imposed in 2001 (66 FR 67485).
- Allow interim marketing of products containing avobenzone with ensulizole and avobenzone with zinc oxide.
- Set an effective date for this final rule other than the 18 months proposed in the 2007 proposed rule.
- Revise the preemption language included in the 2007 proposed rule by deleting any references regarding the rule's potential preemption of State tort law.

Our positions on these issues are discussed in the remainder of this section of the document.

All of the requests to extend the comment period were submitted before the November 28, 2007 **Federal Register** notice in which we extended the comment period of the 2007 proposed rule (72 FR 67264). In that notice, we extended the close of the comment period from November 26, 2007, to December 26, 2007. We have not received any more requests to extend the comment period since December 2007.

With regard to requests to lift the stay of 21 CFR part 352 (the OTC sunscreen monograph), as already discussed, our 2007 proposed rule anticipated amending the testing and labeling provisions of that monograph and subsequently lifting the stay. However, comments received on the 2007 proposed rule not only addressed labeling and effectiveness testing for final sunscreen formulations, but also raised other issues about the monograph conditions for OTC sunscreen products that require further consideration. As a result, we are not finalizing amendments to part 352 at this time nor lifting the stay placed on that section as enacted in 1999 (66 FR 67485). Rather, this final rule establishes in 21 CFR 201.327 labeling requirements and the effectiveness testing upon which it relies for covered OTC sunscreen drug products. We intend to lift the stay on part 352 when we reach our final conclusions on the conditions under which sunscreen products are GRASE and not misbranded, including a determination regarding sunscreen active ingredients, and publish a revised final monograph. In the interim, the labeling and effectiveness testing provisions of this rule apply to covered OTC sunscreen products.

We received a request that we allow interim marketing of avobenzone combinations in proposed § 352.20(a)(2) prior to issuing a final rule for part 352. Subject to our enforcement discretion, we will continue to allow the marketing of avobenzone combinations provided for in the 1999 sunscreen final rule. However, we are not allowing marketing of the additional avobenzone combinations discussed in the 2007 proposed rule until we reach a final conclusion on the GRASE determination for sunscreen active ingredients and combinations of those ingredients.

We are requiring that this final rule become effective in 1 year, even though we considered 18 months in the 2007 proposed rule (72 FR 49070 at 49110). We are allowing products with annual sales less than $25,000 to comply with this rule in 2 years, as stated in the 2007 proposed rule. In response to the proposed rule, we received one submission arguing that we should require this final rule to become effective in 1 year (Ref. 1). The submission stated that a later effective date would have a negative public health impact. We received eight submissions arguing that we should extend the effective date from the proposed 18 months to 3 years (Ref. 1). The submissions listed the following reasons for allowing more than 18 months:

- Repackaging
- Relabeling
- Testing/retesting
- Removing products from market
- Impact on small businesses

The most common argument was that more time would be needed to test/retest OTC sunscreen products for broad spectrum protection in accordance with both the in vitro and in vivo UVA test methods included in the proposed rule.

We agree with the submission which stated that it would be beneficial for consumers to have this rule become effective within 1 year. As explained in section VIII.A of this document, we are not requiring manufacturers to demonstrate broad spectrum protection by conducting in vivo and in vitro tests. This final rule requires that manufacturers conduct only the simpler and less expensive nonclinical in vitro test to demonstrate broad spectrum protection. In vitro tests are substantially shorter than in vivo tests. Therefore, we are setting an effective date for this rule 1 year from the date of publication in the **Federal Register**. However, we are providing two years for all products with annual sales less than $25,000 to comply with this rule. In addition, in order to ensure that limited testing laboratory capacity does not result in sunscreen shortages during the transition to the new rule, we intend to exercise enforcement discretion for a period of time with regard to the SPF test for certain OTC sunscreen products on the market by June 17, 2011 (see our draft guidance entitled ''Guidance for Industry: Enforcement Policy—OTC Sunscreen Drug Products Marketed Without An Approved Application'' announced elsewhere in this issue of the **Federal Register**).

The submissions stating that additional time is necessary for

[2] Nanometers.

repackaging and relabeling did not submit any information or data to support these arguments (Ref. 1). The argument that more than 18 months is needed to remove non-compliant products from the market is not valid. In the 2007 proposed rule, we indicated that sunscreen products which are already distributed by the effective date of the final rule would not be expected to be relabeled or retested in conformity with the final rule conditions unless these products were subsequently relabeled or repackaged after the effective date (72 FR 49070 at 49109). Consistent with this statement, we do not expect non-compliant products introduced or delivered for introduction into interstate commerce prior to the compliance dates specified for this final rule to be removed from the market.

We received a submission that expressed concern about the agency's preemption discussion in the 2007 proposed rule (72 FR 49070 at 49109 and 49110) and requested that we delete any discussion regarding the rule's potential preemption of State tort law (Ref. 1). The submission claimed that we exceeded our authority when we stated that section 751(a) of the FD&C Act displaces both State legislative requirements and State common law duties. The submission argued that Congress intended to preserve State common law claims by including section 51(e), which exempts State product liability claims from express preemption under section 751(a) of the FD&C Act. The commenter appears to have construed our statement in a way that would nullify section 751(e) of the FD&C Act. We did not intend to suggest that section 751(a) of the FD&C Act preempts State product liability claims, whether based on State legislative enactments or common law, because section 751(e) exempts such actions from the express preemption provision in section 751(a). However, it is important to note that section 751(e) of the FD&C Act exempts only those common law claims that are based on State product liability law. Our revised preemption discussion in section XII remains consistent with applicable law.

The submission also requested that we delete any references to implied preemption. In this final rule, we have omitted any statement regarding implied preemption because, although implied preemption may arise, such scenarios are necessarily case-specific. Section XII of this document makes clear that the sole statutory provision giving preemptive effect to the final rule is section 751 of the FD&C Act.

III. Principal Display Panel (PDP) Labeling

In response to the 2007 sunscreen proposed rule, we received 45 submissions requesting that we revise the proposed principal display panel (PDP) labeling (Ref. 1). We are revising the PDP labeling based, in part, on these submissions (see table 1 of this document). We have decided that the PDP labeling included in this document will simplify the purchase decision for consumers by allowing them to more easily find important information included on the PDP.

TABLE 1—SUMMARY OF PDP LABELING IN THE 2007 PROPOSED RULE AND THIS FINAL RULE USING A BROAD SPECTRUM SPF 30 WATER RESISTANT SUNSCREEN PRODUCT AS EXAMPLE A AND AN SPF 6 SUNSCREEN THAT IS NOT BROAD SPECTRUM AND NOT WATER RESISTANT AS EXAMPLE B

Labeled information	2007 Proposed rule	This final rule
Effectiveness Rating [1]	Example A: "UVB SPF 30 High" "UVA ★★★☆ High" Example B: "UVB SPF 6 Low" "No UVA Protection"	Example A: "Broad Spectrum SPF 30" Example B: "SPF 6"
Water Resistance	Example A: "Water Resistant" Example B: No statement on water resistance	Example A: "Water Resistant (40 minutes)" Example B: No statement on water resistance
Educational Statement	Examples A & B: "UV rays from the sun are made of UVB and UVA. It is important to protect against both UVA and UVB rays."	Examples A & B: No educational statement

[1] The UVA rating in the 2007 proposed rule is a four-tier rating (low, medium, high, highest). The UVA testing in this final rule is pass/fail—a product is either allowed or not allowed to include a broad spectrum statement depending on results of the test described in new 21 CFR 201.327(j) (see section VIII of this document).

A. SPF Statement

In the 2007 sunscreen proposed rule, we proposed redefining the acronym ''SPF'' as the ''sunburn protection factor.'' We also proposed that the term ''UVB SPF'' would be required on the PDP of all OTC sunscreen products (proposed 21 CFR 352.50(a)). This term would be followed by the numerical value determined from SPF testing and one of the following descriptors: ''low,'' ''medium,'' ''high,'' or ''highest.'' For example, a sunscreen product could have contained the statement ''UVB SPF 40 High'' on the PDP.

We received 12 submissions regarding the SPF statement in response to the 2007 sunscreen proposed rule (Ref. 1). Collectively, the submissions made the following requests:

1. Do not change the definition of SPF to ''sunburn protection factor''
2. Remove UVB from ''UVB SPF''
3. Redefine the ''highest'' product category descriptor to include SPF 50
4. Require SPF values expressed in multiples of 5
5. Label SPF as the percent of UVB radiation screened

As discussed in the remainder of this section, we agree with the first and second requests, but are not granting the other three requests.

In this final rule, unlike the 2007 proposed rule, we have no express definitional section. However, we identify ''SPF'' as an abbreviation for ''sun protection factor'' in new 21 CFR 201.327(a)(1), and use it consistently in this way throughout the rule. This use of the term SPF is identical to the definition in the 1999 stayed sunscreen final rule (64 FR 27666). For products that are not broad spectrum, the term ''SPF'' will appear on the PDP with the numerical SPF value calculated according to the test method in new 21

CFR 201.327(i). For broad spectrum sunscreen products, the term ''Broad Spectrum SPF'' will appear on the PDP along with the numerical SPF value calculated according to the test method in new 21 CFR 201.327(i).

The term ''UVB'' will not be required as part of the SPF statement. We are also not requiring the descriptor (*e.g.,* ''high'' or ''low''). We included these two requirements in the 2007 proposed rule because we had concluded that the requirements would help consumers understand the side-by-side SPF numerical rating in conjunction with the UVA star rating, which included the term ''UVA'' and the same descriptors (72 FR 49070 at 49084). As discussed in section III.B of this document, the UVA star rating is not being included in this final rule, and as discussed below, we have concluded that neither the term ''UVB'' nor the descriptor is necessary for consumers to understand the effectiveness statement.

Neither the term ''UVB'' nor a descriptor (*e.g.* ''low'' or ''high'') had been included on sunscreen labels prior to our 2007 proposal, and consumers had been able to make purchase and use decisions based on SPF values alone. Under this final rule, the SPF value will be expressed on the PDP by including the term ''SPF,'' followed by the numerical value determined from the SPF test, similar to how it has appeared on the labels of OTC sunscreen products for more than 30 years. As described in section III.B of this document, for products passing the critical wavelength test in new 21 CFR 201.327(j), the SPF value statement will be expressed as ''Broad Spectrum SPF'' followed by the numerical SPF value calculated according to the test method in 21 CFR 201.327(i).

We received five submissions objecting to the definition of SPF as ''sunburn protection factor'' and only one submission supporting the definition (Ref. 1). The submissions objecting to the definition argued that, if the term ''sunburn protection factor'' is used, consumers may mistakenly assume that a higher SPF value means a higher probability of sunburn. Additionally, they argued that sunscreen products protect against various harmful effects of sun exposure, such as early skin aging and skin cancer, in addition to protecting against sunburn. Some submissions suggested that the term ''sunburn protection factor'' will lead consumers with darker skin to assume that they do not need sunscreen products because they do not burn easily (Ref. 1).

We agree with the arguments provided by the submissions suggesting that the term ''sunburn protection factor'' may be misleading. In the 2007 sunscreen proposed rule, we revised the definition of SPF from ''sun protection factor'' to ''sunburn protection factor'' because we thought that the new definition was more descriptive of what an SPF value represents (72 FR 49070 at 49077). The SPF value is determined from a clinical test with sunburn as the endpoint. However, for broad spectrum sunscreen products, the SPF statement also serves as a relative measure of the magnitude of broad spectrum protection (Ref. 4). In this final rule, while we do not codify a separate definitional section, we continue to use the term ''SPF'' to mean ''sun protection factor,'' as we had done in the 1999 final rule (21 CFR 201.327(a)(1)).

In this final rule, we are also revising the effectiveness statement so that the term ''UVB'' is not required before the term ''SPF,'' as proposed in the 2007 proposed rule (proposed 21 CFR 352.50(a)). We received six submissions requesting this revision (Ref. 1). These submissions argued that ''UVB SPF'' is an incorrect representation of the SPF value determined from a test using a solar stimulator that emits both UVA and UVB radiation. The submissions point out that sunburn is not caused solely by UVB radiation. It is well known that UVA radiation contributes up to 20 percent of the skin's sunburn response (Refs. 5 and 6). One submission points out that if a sunscreen product blocked 100 percent of the incident UVB radiation and none of the erythemally effective UVA radiation, the sunscreen product would have SPF values no higher than 11 (if only 9 percent or 1/11 of UV radiation reaches the skin) (Ref. 4).

We agree that UVA radiation contributes to the development of sunburn. Although the contribution of UVA to sunburn is less than UVB, it is still significant (Ref. 5). Further, as stated in the submissions, protection against UVA radiation is necessary to achieve higher SPF values (Ref. 5). We proposed including the term ''UVB'' in the SPF statement in the 2007 proposed rule to help consumers understand that the SPF effectiveness rating is different from the UVA effectiveness (star) rating being proposed (72 FR 49070 at 49084). However, as discussed elsewhere in this final rule we are not requiring a UVA effectiveness rating on the PDP (see section III.B.). Therefore, the term ''UVB'' is not necessary as part of the SPF statement. In this final rule, we are not requiring the term ''UVB'' be placed before the term ''SPF.''

In the 2007 sunscreen proposed rule, we stated that the SPF value should be followed by one of the descriptors ''low,'' ''medium,'' ''high,'' or ''highest'' (proposed 21 CFR 352.50(a)). The proposed descriptors were included to help consumers understand the SPF value because the label would have included identical descriptors for the UVA star rating. As discussed in section III.B. of this document, we are not requiring a UVA effectiveness rating on the PDP. Therefore, descriptors are no longer required to distinguish the SPF value from the UVA rating on a sunscreen label. Because we are not requiring a descriptor after the SPF value on the PDP in this document, the request to include SPF 50 sunscreen products in the ''highest'' category is no longer relevant.

We received two other requests for revision to the SPF statement with which we do not agree. First, a submission stated that SPF values should only be labeled in multiples of five to be consistent with SPF labeling recommendations by the European Commission (Ref. 7). Second, one request from a submission suggested that SPF values should be expressed as the percent of UV absorption. The submission argued that the current SPF values are misleading because consumers believe an SPF 15 sunscreen product is not very protective even though it screens 93 percent of UV radiation.

We do not agree with either submission. Based on SPF test data we have reviewed, we find that SPF values for sunscreen products generally can be determined with a precision that allows the products to be labeled with SPF values in intervals of less than 5 units (Ref. 1). Therefore, there is no mathematical or statistical basis for restricting SPF values to multiples of five. Contrary to the second request, consumers have relied on SPF values for over 30 years and are familiar with this format. Therefore, expressing SPF values as percentages may be confusing. It would imply that the stated percentage of the entire UV spectrum is absorbed by a sunscreen. However, the SPF values only reflect protection against the portion of the UV spectrum that causes sunburn. Additionally, the percentages of UV radiation screened that the submission notes are theoretical. The percentages are determined in a laboratory setting and not under actual use conditions. For example, laboratory tests may show that an SPF 15 sunscreen absorbs 93 percent of UV rays, but, under actual use conditions, the level of protection provided by an SPF 15 sunscreen product may be significantly below 93 percent. There are a number of factors

that lead to this decreased protection, the most important being under-application of the sunscreen product (72 FR 49070 at 49092). Therefore, if SPF values were expressed as percentages, consumers might mistakenly believe that the sunscreen products they are using provide more protection than they really do provide under actual use conditions.

B. Broad Spectrum Statement

In response to the 2007 proposed rule, we received over 50 submissions collectively making the following four requests regarding the UVA effectiveness rating (Ref. 1):

1. Do not require UVA 4-star rating system.
2. Do not require ''no UVA protection'' statement if a product does not protect against UVA radiation.
3. Do not require the UVA statement to be the same size as the SPF statement.
4. Perform label comprehension studies prior to implementing proposed PDP labeling.

The submissions included arguments, but no data, to support these requests.

We agree with the first and second requests. However, we are not granting the third and fourth requests. Our reasons for these decisions are explained below, but we first summarize the related provisions of this final rule. We are not requiring a star rating or descriptors to indicate the level of UVA protection as proposed. Instead, to indicate the level of UVA and UVB protection, we are establishing a pass/fail broad spectrum test and a broad spectrum labeling statement. If a sunscreen product passes the broad spectrum test (see section VIII.B. of this document), under this final rule, the PDP of the product must include the statement ''Broad Spectrum SPF [insert numerical SPF value resulting from testing under paragraph (i) of this section],'' without any ''UVA'' reference (§ 201.327(a)(1)(i)). We are requiring the Broad Spectrum SPF statement to appear as continuous text with no intervening text or graphics. We are also requiring that the entire text be the same font style, size and color on the same background color. (§ 201.327(a)(1)(ii)).

With regard to the submissions received, nearly all of the 50+ submissions argued against requiring the 4-star rating system to display the level of UVA protection on the PDP of OTC sunscreen products (Ref. 1). Many submissions stated that the presence of stars and a number (SPF) on the PDP will lead to consumer confusion. Some submissions argued that consumers may be confused when determining whether a star is filled or empty, thereby not knowing the UVA protection level. Other submissions argued that consumers are familiar with star ratings, but that the star rating for items such as movies and hotels are based on recommendations and not rigorous data. They suggested several options for labeling UVA protection, such as a numerical rating or another symbol other than stars.

Some submissions suggested that the UVA rating should be proportional to the SPF value but requested that there not be two ratings on the PDP. The submissions cited the European Commission's recommendation that UVA protection increase as the SPF value increases (Ref. 7). The European Commission recommends a minimum UVA protection factor equal to at least one-third of the labeled SPF or a critical wavelength of at least 370 nm, but does not recommend that the actual value of the UVA protection factor or critical wavelength be displayed. The European Commission recommends that the main indicator of sun protection be the SPF value. Broad spectrum protection is indicated by a symbol on sunscreen labels—the acronym ''UVA'' enclosed within a circle the diameter of which should not exceed the height of the SPF value.

We agree with the submissions that the UVA star rating would likely be confusing in conjunction with the numerical SPF rating. We also agree with the submissions requesting that UVA protection should be proportional to the SPF value. We are requiring such proportionality in the broad spectrum test described in this document. Because of this proportionality, there is no longer a need for a separate UVA rating. Instead of a rating, we are requiring a ''broad spectrum'' statement on the PDP if a product has a critical wavelength equal to or greater than 370 nm. This pass/fail ''broad spectrum'' statement is consistent with the recommendations in the submissions citing the recommendations of the European Commission.

As noted, several submissions responding to our proposal for a separate UVA rating with stars suggested that consumer comprehension testing should be performed before the proposed labeling is implemented. We agree with the submissions that consumer comprehension data can be very helpful in formulating labeling changes. In fact, in conjunction with our 1993 proposal to allow products to be labeled as ''broad spectrum'' if they contained sunscreen active ingredients that absorbed UVA radiation (58 FR 28194 at 28233), we requested label comprehension study data to allow us to determine consumer understanding of the terms ''broad spectrum,'' ''UVA,'' and ''UVB'' (58 FR 28194 at 28243). Unfortunately, the data we received were not sufficient to allow us to determine the level of consumer understanding of these terms (72 FR 49070 at 49081 through 49085), and we received no further consumer comprehension data in response to the 2007 proposal to require the UVA star rating. While we acknowledge the value of consumer comprehension data, for reasons explained below, we conclude that conducting consumer comprehension testing is not necessary in this case in light of the labeling we have selected for the final rule.

First, submissions suggesting consumer testing were responding to the UVA star rating in the proposed rule, the value of which would have been based on the results of two tests (72 FR 49070 at 49081 through 49085). As noted, we agree with the submissions suggesting that the 2007 UVA labeling proposal was likely to be confusing. Elsewhere in the document, we also discuss our final choice of a pass-fail test for establishing UV protection (section VIII.B). As a result of these changes in the underlying test method and the submissions on the proposed labeling, we have incorporated a much simpler labeling statement in this final rule. This statement designates as ''broad spectrum'' those products that are demonstrated to have a critical wavelength of at least 370 nm, using the test in new 21 CFR 201.327(j).

Second, unlike in 1993 when we first sought consumer data on the term ''broad spectrum'', and unlike the UVA star rating that we proposed in 2007, consumers are now likely to be familiar with the term ''broad spectrum'' as included in this document because some sunscreen manufacturers have labeled sunscreen products as ''broad spectrum'' for over 20 years. For example, the Johnson and Johnson ''Sundown Broad Spectrum'' line of sunscreens was on the market in 1988 (Ref. 8). As already noted, in our 1993 proposed rule, we not only sought consumer data, but in fact proposed that products be permitted to be labeled as ''broad spectrum'' if they contained sunscreen active ingredients that absorbed UVA radiation, although we did not at that time propose to require a specific test to demonstrate UVA protection (58 FR 28194 at 28233). We continued to allow this statement in the 1999 sunscreen final rule (64 FR 27666 at 27666 through 27667).

Many consumers may also be familiar with the term ''broad spectrum'' because

of public health campaigns and news articles about the importance of broad spectrum UV protection over the last two decades. For example, an article appearing in Working Woman magazine in 1990 urged women to ''make sure to look for the term 'broad spectrum' on the label of a sunscreen'' because ''it means you're getting protection from both types of radiation'' (Ref. 9).

For consumers not already familiar with the term ''broad spectrum,'' the additional indication statement allowed in this document for certain broad spectrum sunscreen products should help consumers recognize the benefit of these products. Under ''Uses'' in Drug Facts, broad spectrum sunscreen products with an SPF value of 15 or higher are allowed the following indication statement: ''if used as directed with other sun protection measures (see Directions [in bold italic font]), decreases the risk of skin cancer and early skin aging caused by the sun'' (new 21 CFR 201.327(c)(2)).

In addition, educational campaigns about sun protection will further inform consumers about the benefits of using sunscreens that include the term ''broad spectrum'' on their labels and have an SPF value of 15 or higher. We expect consumers to learn that a sunscreen labeled with the statement ''Broad Spectrum SPF'' 15 or higher, when used as directed with other sun protection measures, offers more comprehensive protection against sun-induced skin damage than that provided by a sunscreen that is not broad spectrum or that are broad spectrum with an SPF value less than 15.

It is important to note that the broad spectrum test required in this document captures both UVB and UVA protection for the effectiveness of a sunscreen product. The broad spectrum test is not limited to UVA wavelengths as was the case with the proposed test (see section VIII.B of this document). By requiring that a broad spectrum sunscreen provide both UVB and UVA protection in a pass/fail test, the amount of UVA protection for a sunscreen product that passes the test must increase as the SPF increases. For example, a Broad Spectrum SPF 40 sunscreen product provides greater protection against both UVB and UVA than a Broad Spectrum SPF 20 sunscreen product. In contrast, an SPF 40 sunscreen product that is not broad spectrum provides more UVB protection than a SPF 20 sunscreen product that is not broad spectrum, but may not provide more UVA protection.

This proportionality between UVB and UVA protection is important because consumers have been accustomed to basing their purchase decision concerning protection level primarily on the SPF value, and only secondarily on indications of whether or not the sunscreen provides broad spectrum protection. For example, a consumer seeking lower protection may have chosen an SPF 15 sunscreen product, whereas a consumer seeking higher protection may have chosen an SPF 40 sunscreen product. By creating a clear and standardized ''yes/no'' indicator regarding broad spectrum protection, these final labeling requirements will enable consumers to make better and more informed purchase decisions by looking to see if a product has a ''Broad Spectrum SPF'' value on the label. Thus, the ultimate purchase decision would be based on the numerical value associated with the Broad Spectrum SPF statement. For products offering broad spectrum protection, the Broad Spectrum SPF value on the PDP will not only indicate the relative level of protection against UVB radiation but will also reflect the level of UVA protection, with increasing SPF values indicating greater protection against both UVA and UVB radiation. For broad spectrum products, linking the amount of UVA protection to the SPF value, is consistent with the approach taken in Europe (Ref. 7).

For broad spectrum products, we are requiring the broad spectrum statement on the PDP to appear in combination with the SPF statement. For example, an SPF 40 sunscreen product which passes the broad spectrum test will be labeled ''Broad Spectrum SPF 40'' in a uniform font style, size, and color and with the same background color. This placement will help consumers recognize that the particular sunscreen product is broad spectrum in conjunction with the SPF value. As previously explained, the broad spectrum statement and SPF value together will provide a relative measure of both UVB and UVA protection. Combining the broad spectrum and SPF statements will help consumers become more aware of the importance of broad spectrum protection.

Under the 2007 proposed rule, if an OTC sunscreen product was not tested for or did not protect against UVA radiation, the statement ''No UVA protection'' would have been required on the PDP (proposed 21 CFR 352.50(b)(1)). Ten submissions argued against requiring this statement (Ref. 1). Some submissions argued that this statement is misleading because all sunscreen products provide some UVA protection. Submissions also stated that a negative statement is inconsistent with the OTC Drug Review because a drug should only describe the indications for which it is effective. Other submissions suggested that we should require all sunscreen products to provide UVA and UVB protection, making this statement unnecessary.

We have concluded that the ''No UVA Protection'' statement is not necessary and could be misleading. Under this final rule, the labeling on the PDP of sunscreens no longer refers the type of UV radiation (UVA or UVB) protection offered; rather, products that pass the critical wavelength test in 201.327(j) are labeled with ''Broad Spectrum SPF'' values. Under this labeling, consumers who see ''UVA'' on the PDP, even if it is part of the statement ''No UVA Protection,'' may mistakenly believe that the product offers UVA protection. To eliminate this potential misunderstanding, we are not including the ''No UVA Protection'' statement on the PDP.

In contrast to four submissions requesting that we make the UVA statement less prominent than the SPF statement, we are requiring the SPF and broad spectrum statements to be equally prominent on the PDP by appearing as a combined statement. The four submissions stated that they believe UVB radiation contributes more to skin cancer and photodamage than UVA radiation and argued that more prominence should be given to the SPF statement. However, none of the submissions included data to support this argument. Some submissions suggested that consumers are familiar with SPF ratings and that providing another rating with similar prominence may mislead and confuse consumers.

It is well known that both UVA and UVB radiation contribute to photodamage and skin cancer (Refs. 6–7 and 10–12). Therefore, in our view, providing consumers with information about the effectiveness of a sunscreen product for UVA and UVB radiation protection is equally important. We are requiring that the broad spectrum statement be displayed in combination with the SPF statement. The two statements must not be interrupted with any graphics or text. In addition, the broad spectrum statement must be the same font style, size, and color as the SPF statement with the same background color. It is important for consumers to evaluate both statements when making a purchase decision. By requiring this information to be presented with identical prominence on the PDP, consumers should be able to quickly and easily identify sunscreen products that provide broad spectrum protection, as well as the SPF of all sunscreen products. While we are not requiring a negative statement on the

PDP of products that do not pass the critical wavelength test in new 301.327(j), we caution that such products may be misbranded if they include statements regarding UVA protection; such statements may misleadingly imply that the product provides benefits that are similar or superior to those of products labeled with Broad Spectrum SPF values.

C. Water Resistance Statement

In the 2007 sunscreen proposed rule (proposed 21 CFR 352.52), we allowed the PDP of OTC sunscreen products to contain the statement ''water resistant'' if a sunscreen product was shown to retain the labeled SPF value after 40 minutes of water immersion, or ''very water resistant'' if a sunscreen product was shown to retain the labeled SPF value after 80 minutes of water immersion, according to the test in proposed 21 CFR 352.76. We simultaneously proposed that the ''Uses'' section of labeling (not the PDP) indicate specifically whether the product had been established to be water resistant for 40 minutes or 80 minutes, and included specific directions addressing times for reapplication of each product, dependent on its level of water resistance (proposed 21 CFR 352.52(b)(1)(vii), (b)(1)(viii), (d)(2), and (d)(3); 72 FR 49070 at 49113). In this document, we are revising the PDP to contain the statement ''water resistant (40 minutes)'' or ''water resistant (80 minutes)'' as determined by the water resistance test in new 21 CFR 201.327(i)(7). We are removing this information from the indications section of Drug Facts (section IV.B of this document). We continue to include directions based on the duration of water resistance established under the new water resistance test (section IV.D of this document).

One submission stated that including information about water resistance in the indications section as well as in the directions section is ''redundant and confusing'' (Ref. 1). The submission recommended that we delete the indications statement. We agree with the submission. To eliminate redundancy and simplify the labeling for consumers, we are relocating the information formerly contained within the indication statement to the PDP.

The content of the labeling as a whole is the same as that included in the 2007 proposed rule. However the proposed statement on the PDP did not clearly and accurately convey to consumers the difference between ''water resistant'' and ''very water resistant'' sunscreen products. For example, knowing that a sunscreen product is ''very water resistant'' does not give any indication of how much time a consumer can safely spend in the water. Under the 2007 proposed rule, a consumer would have had to read either the ''Uses'' or the ''Directions'' section of the Drug Facts label to determine the duration of water resistance for a sunscreen product (proposed 21 CFR 352.52(b)(1)(vii) and (b)(1)(viii) and proposed 21 CFR 352.52(d)(2) and (d)(3), respectively; 72 FR 49070 at 49113).

Providing, on the PDP, specific information about the actual time (40 or 80 minutes) a consumer can expect a sunscreen product to retain its labeled SPF value is likely to be more helpful to consumers because the information is displayed in one place—on the PDP and not on different parts of the labeling. The revised statements ''water resistant (40 minutes)'' or ''water resistant (80 minutes)'' should make it clearer and easier for consumers to understand water resistance as part of their purchase decision. This water resistance information continues to be reinforced by information in the directions regarding reapplication.

D. UVB and UVA Educational Statement

In the 2007 sunscreen proposed rule, we proposed that the following educational statement be included on the PDP of all OTC sunscreen products (proposed 21 CFR 352.50(c)): ''UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB and UVA rays to prevent sunburn and other skin damage.''

We received four submissions regarding the UVB and UVA educational statement in response to the 2007 sunscreen proposed rule (Ref. 1). The submissions made the following requests:

- Do not require the educational statement on the PDP or
- Combine the educational statement with the sun alert statement and include the combined statement in the ''Other Information'' section of the Drug Facts label.

We considered including the proposed educational statement on the PDP. We concluded that this information is not critical for effective use of sunscreen products, particularly since we are no longer requiring other PDP statements to refer separately to UVA and UVB protection. An understanding that the sun produces ultraviolet (UV) rays or that there are two types of UV rays that reach the earth's surface is not necessary to ensure the safe and effective use of sunscreen products. The explanation of these concepts on sunscreen labeling is potentially confusing and could raise additional questions about their meaning. We could not determine a succinct educational statement that would not also be potentially misleading. Therefore, we have concluded that an educational statement should not be required on the PDP.

As noted, submissions also requested that the proposed educational statement be combined with proposed sun alert, included in the proposed rule as a warning. In section IV.C of this document, we address submissions on the sun alert warning, and explain our decision to incorporate the information regarding the role of certain sunscreens in reducing the risk of skin cancer and early skin aging into a new indication and accompanying directions for sunscreens with Broad Spectrum SPF values of 15 or higher. We are retaining a modified warning to be included as the first warning on sunscreen products that are either not broad spectrum or that are broad spectrum with an SPF value less than 15. Because we are not requiring an educational statement on the PDP and are either eliminating or modifying the proposed sun alert warning, the request to combine these two statements is no longer relevant.

IV. Drug Facts Labeling

In September 2004 (69 FR 53801), we delayed the May 16, 2005, implementation date for the Drug Facts final rule (21 CFR 201.66) for OTC sunscreen products until further notice). The Drug Facts final rule (21 CFR 201.66) establishes general labeling format and content requirements for all OTC drugs. With the additional exception of certain OTC drug products in ''convenience size'' packages (see 67 FR 16304 at 16306 (April 5, 2002), other OTC drug products are already required to comply with 201.66. We delayed implementation of 201.66 for sunscreens so as to avoid the potential that sunscreen manufacturers would have to relabel their products twice within a short time period if a final rule specifying labeling for sunscreens published shortly after the original May 2005 implementation date for the general content and format requirements of the Drug Facts final rule. We published the notice of delay for OTC sunscreens' implementation of the Drug Facts final rule so that such products could simultaneously implement both the general labeling provisions of that rule and the specific labeling provisions for sunscreens when we published a sunscreen labeling final rule. We are now lifting the stay on the implementation of the Drug Facts final

rule for OTC sunscreen products. In this document, we are requiring the same implementation date for the regulations set forth in this labeling and testing final rule (21 CFR 201.327) and in the Drug Facts final rule (21 CFR 201.66) as applied to these sunscreen products.

This action will benefit both consumers and manufacturers. Consumers will benefit by having sunscreen labeling presented in the Drug Facts format that they are familiar with. Manufacturers benefit because they will achieve compliance with two rules through one labeling revision (rather than following the more expensive course of making two labeling changes at two different times).

In 2003 (68 FR 33362, June 4, 2003), we also stayed the part of the skin protectant monograph that describes GRASE combinations of skin protectant and sunscreen active ingredients (21 CFR 347.20(d)). Because this document addresses the labeling and testing of sunscreen products and not the GRASE status of individual sunscreen active ingredients, we are not lifting the stay of 21 CFR 347.20(d).

This document requires much of the Drug Facts labeling included in the 2007 proposed rule. However, we have made several revisions to the proposed labeling. These revisions are discussed in detail throughout the remainder of this section. In addition, table 2 of this document summarizes these revisions as follows:

TABLE 2—SUMMARY OF DRUG FACTS LABELING INCLUDED IN THE 2007 PROPOSED RULE AND THIS FINAL RULE

Drug facts section	2007 Proposed rule	This final rule
Active Ingredients/ Purpose.	Name and amount of ingredient(s) followed by "sunscreen"	Name and amount of ingredient(s) followed by "sunscreen."
Uses	• [low, medium, high, or highest] UVB sunburn protection • [low, medium, high, or highest] UVA protection • retains SPF after 80 minutes of activity in the water	• for all sunscreen products: "helps prevent sunburn." • Optional, for sunscreen products with Broad Spectrum SPF values of 15 or higher, "if used as directed with other sun protection measures (see Directions), decreases the risk of skin cancer and early skin aging caused by the sun."
Warnings	*UV exposure from the sun increases the risk of skin cancer, premature skin aging, and other skin damage. It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen.* *For external use only* *Stop use and ask a doctor if* skin rash occurs *When using this product* keep out of eyes. Rinse with water to remove. *Keep out of reach of children.* If swallowed, get medical help or contact a Poison Control Center right away.	For sunscreen products that are not broad spectrum or for products that are broad spectrum with an SPF value less than 15, Skin Cancer/Skin Aging Alert [in bold font]: Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, not [in bold font] skin cancer or early skin aging. For all sunscreens: *For external use only* *Do not use* on damaged or broken skin *Stop use and ask a doctor if* rash occurs *When using this product* keep out of eyes. Rinse with water to remove. *Keep out of reach of children.* If swallowed, get medical help or contact a Poison Control Center right away.

Directions	*Non-Water Resistant Product*
	• apply liberally [# minutes] before sun exposure
	• reapply at least every 2 hours and after towel drying, swimming, or sweating
	• apply and reapply as directed to avoid lowering protection
	• children under 6 months: Ask a doctor
	Water Resistant Product
	• apply liberally [# minutes] before sun exposure
	• reapply after 40 [or 80] minutes of swimming or sweating and after towel drying. Otherwise, reapply at least every 2 hours.
	• apply and reapply as directed to avoid lowering protection
	• children under 6 months: Ask a doctor
	Water Resistant and Non-Water Resistant Products
	No statement
		Non-Water Resistant Product
		• apply liberally 15 minutes before sun exposure
		• use a water resistant sunscreen if swimming or sweating
		• reapply at least every 2 hours
		• children under 6 months: Ask a doctor
		Water Resistant Product
		• apply liberally 15 minutes before sun exposure
		• reapply:
		  • after 40 [or 80] minutes of swimming or sweating
		  • immediately after towel drying
		  • at least every 2 hours
		• children under 6 months: Ask a doctor
		Water Resistant and Non-Water Resistant Products
		For sunscreens with Broad Spectrum SPF values of 15 or higher:
		• Sun Protection Measures [in bold font]. Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a Broad Spectrum SPF value of 15 or higher and other sun protection measures including:
		  • limit time in the sun, especially from 10 a.m.–2 p.m.
		  • wear long-sleeved shirts, pants, hats, and sunglasses.

Inactive Ingredients	List inactive ingredients in alphabetical order	List inactive ingredients in alphabetical order.
Other Information	No required statements	• protect this product from excessive heat and direct sun.
Questions?	No required statements	No required statements.

A. Active Ingredients/Purpose

We received one submission regarding the listing of active ingredients and one submission requesting that we provide specific details about what each ingredient does in the product (Ref. 1). One of these submission also requested that we require listing of the percentage of each active ingredient next to the ingredient name.

We are not making any changes to the ''Active ingredients/Purpose'' section of the Drug Facts label. The general OTC labeling regulations specify that the ''quantity of each active ingredient per dosage unit'' be listed with the established name of each active ingredient (21 CFR 201.66(c)(2)). Therefore, every sunscreen product is already required to include the active ingredient names followed by the percentage (weight per volume) in the ''Active ingredients/Purpose'' section, as requested by the first submission.

We are not requiring specific details about what each ingredient does in the product. The function of each active ingredient in an OTC drug product is already required to be listed by 21 CFR 201.66(c)(3), which specifies that the ''Active ingredients/Purpose'' section of the label list the ''general pharmacologic categories or principal intended actions of each active ingredient.'' There is not currently a requirement to list the purpose of inactive ingredients on OTC drug labels. This information is not needed to safely and effectively use sunscreen products. Therefore, in this document, we are not requiring the purpose of inactive ingredients to be listed on sunscreen labels.

B. Uses

1. Indications Statements Proposed in the 2007 Proposed Rule

The 2007 proposed rule included three indication statements under ''Uses'' in Drug Facts:

1. Level of UVB sunburn protection (proposed 21 CFR 352.52(b)(1)(i)–(b)(1)(iv))
2. Level of UVA protection (proposed 21 CFR 352.52(b)(1)(v) and (b)(1)(vi))
3. Extent of water resistance (proposed 21 CFR 352.52(b)(1)(vii) and (b)(1)(viii))

The first statement would have appeared on all monograph sunscreen products. The second statement would only have appeared on monograph sunscreen products providing UVA protection. The third statement would only have appeared on monograph sunscreen products that are water resistant for either 40 or 80 minutes. We received numerous submissions from the public concerning these statements following publication of the 2007 proposed rule (Ref. 1).

We are not requiring these indication statements in this final rule. Instead, all sunscreen products covered by this rule will be required to include the indication statement ''helps prevent sunburn,'' as required in the 1999 sunscreen final rule (64 FR 27666; new 21 CFR 201.327(c)(1)). We are requiring this statement instead of the first proposed statement (level of UVB sunburn protection) because we agree with submissions arguing that sunburn is not caused solely by UVB radiation (Ref. 1). We also agree with submissions arguing that the SPF value by itself on the PDP informs consumers of the level of sunburn protection, so a separate description of the level of sunburn protection does not need to be included as an indication.

In addition, sunscreen products covered by this rule that provide broad spectrum protection according to the test in new 21 CFR 201.327(j) and have SPF values of 15 or higher, may include the following indication statement (new 21 CFR 201.327(c)(2)(i)): ''if used as directed with other sun protection measures (see Directions), decreases the risk of skin cancer and early skin aging caused by the sun.'' This statement replaces the second proposed indication statement. We are allowing this statement for certain sunscreens covered by this rule based on available clinical studies, the fact that UV radiation from the sun is harmful, and the scientific understanding that substantially limiting overall UVB and UVA exposure reduces the risk of skin cancer and early skin aging.

As discussed in the remainder of this section of the document, it is critical that the indication statement regarding skin cancer and early skin aging includes information about using the products as directed and following other sun protection measures (listed under the heading Directions). We have concluded that the reference to other sun protection measures is necessary to ensure that the consumer's overall UV exposure is substantially decreased. A consumer who relies on the use of a sunscreen with Broad Spectrum SPF value of 15 or higher alone may not obtain a meaningful net decrease from the risk of skin cancer or early skin aging if, because he or she is wearing the sunscreen, the consumer spends more time in the sun and/or wears less protective clothing. In fact, reliance on sunscreen use alone, without also employing other sun protection measures, could actually result in an increase in the consumer's overall UV exposure. Therefore, if the indication statement regarding decreasing risk of skin cancer and early skin aging does not include the information about using the product as directed, which includes following other sun protection measures, the statement will be considered misleading (and thus make a sunscreen product misbranded) (new 21 CFR 201.327(c)(3)). Similarly, sunscreen products covered by the rule that provide broad spectrum with SPF values between 2 and 15 or do not provide broad spectrum protection should not state or imply that the use of a sunscreen product alone will reduce the risk of skin cancer or early skin aging. Doing so would cause the product to be misbranded.

We are not including the third proposed indication statement (regarding water resistance) in this document. As already discussed, under this final rule, information about water resistance is included on the PDP, as well as under ''Directions'' in Drug Facts (see sections III.C and IV.D of this document). We conclude that information about the water resistance of a sunscreen product is more effectively and accurately presented on the PDP and as a direction than as an indication statement. The extent of water resistance informs a consumer about how long the SPF value is retained following water exposure and, therefore, how long an interval can elapse before reapplying the sunscreen product (40 or 80 minutes). In addition, the PDP requirements in this document include the time interval as part of the water resistance statement, so that consumers can readily distinguish between products on this basis when making purchasing decisions. Because we include water resistance on the PDP and under ''Directions,'' we are not including a separate indication statement about water resistance in this document.

2. Statement Regarding Skin Cancer and Early Skin Aging

a. Submissions Arguing For a Skin Cancer and Early Skin Aging Indication

As already stated, in this final rule we have adopted, for the first time, an indication for skin cancer and early skin aging for sunscreen products covered by the rule that have Broad Spectrum SPF values of 15 or higher. In our 2007 proposed rule, we had included indication statements that indicated the degree of protection against both UVB and UVA radiation but that linked UVB protection only to sunburn prevention and did not expressly link UVA

protection to any specific health benefit (proposed 21 CFR 352.52(a)). At the same time, however, we had proposed both an educational statement on the PDP stating that UV rays from the sun are made of both UVB and UVA and that it is important to protect against both types of radiation to prevent sunburn and other skin damage (proposed 21 CFR 352.50 (c)). We also proposed a ''sun alert'' statement as the first warning. This first warning read, ''UV exposure from the sun increases the risk of skin cancer, premature skin aging, and other skin damage. It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen.'' (proposed 21 CFR 352.52(c)(1)).

In response to our proposed rule, we received a total of 12 submissions asking that we include a specific statement regarding reduction in risk of skin cancer and early skin aging as an indication for covered sunscreens (Ref. 1). The submissions asked that we allow an indication statement informing consumers that the regular, consistent, or continued use of a sunscreen product reduces or helps reduce the risk or chance of developing skin damage, early skin aging, and some types of skin cancer (Ref. 1). These submissions also supported our proposed requirement of a ''sun alert'' on the labeling to inform consumers of the need to limit time in the sun and wear protective clothing. The submissions came from sunscreen manufacturers and public health organizations including the American Academy of Dermatology, the American Cancer Society, and the Skin Cancer Foundation. Many of the submissions provided references to studies that they argued support the inclusion of this indication statement. One submission specifically requested that we allow an anti-aging claim (without mention of skin cancer), and one other submission argued that no sunscreen can claim to prevent cancer (Ref. 1). We received no new data to accompany these requests for a separate indication that the regular use of sunscreen decreases the risk of skin cancer and early skin aging. However, on reconsideration of the data reviewed prior to the 2007 proposed rule, we agree with the argument that the data underpinning our proposed education statement and warning are sufficient to support an appropriately qualified skin cancer and premature skin aging indication for one subset of sunscreens covered by this rule—those that have Broad Spectrum SPF values of 15 or higher. As a result, our final rule provides different labeling for these sunscreens than for sunscreens covered by the rule that are not broad spectrum or that provide broad spectrum with SPF values less than 15. In addition, we conclude that such an indication should not be included in the Warnings section of Drug Facts. We have concluded that, as proposed in 2007, the second sentence of the first warning (*i.e.,* the ''Sun Alert'' warning) is an implied indication: ''It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen.'' Because it follows a warning that ''UV exposure from the sun increases the risk of skin cancer, premature skin aging, and other forms of skin damage,'' the second sentence implies that using any sunscreen, regardless of SPF value or broad spectrum protection, and following other sun protection measures will decrease the risks of skin cancer, early skin aging, and other consequences of UV exposure to the sun. We have concluded, based on a reconsideration of data previously reviewed in the 2007 proposed rule, that, if consumers use broad spectrum sunscreens with SPF values of 15 or higher and follow other sun protection measures, they can reduce their risk of skin cancer and early skin aging. For these products, we agree with the public submissions that this information is most appropriately placed as an indication (*i.e.,* under Uses) with a reference to the need to use the product as directed with other sun protection measures. For these products, we include under the heading Directions, specific reference not only to regularly use sunscreens with Broad Spectrum SPF values of 15 or higher (the subset of sunscreens for which the indication is allowed) but also to employ the other listed sun protection measures listed under Directions. For sunscreen products covered by this rule that are not Broad Spectrum or that are broad spectrum with an SPF value less than 15, however, we conclude that existing data are insufficient to support an indication for reducing risk of skin cancer or early skin aging. In the sections that follow, we explain the specific scientific basis for our conclusion, as well as explain our rationale for the specific framing of the labeling, as included in the final rule, for both subsets of the sunscreens covered by the final rule—those that have Broad Spectrum SPF values of 15 or higher and those that do not have Broad Spectrum or that are Broad spectrum with SPF values less than 15.

b. Limiting Overall UV Exposure Reduces Risk of Skin Cancer and Early Skin Aging

For drugs subject to OTC monographs, like sunscreen products, indication statements about the effectiveness of the drug products must be supported with scientific data (21 CFR 330.10(a)(4)(ii)). In order for an OTC drug to be considered generally recognized as effective (GRAE), there must be a reasonable expectation that, in a given proportion of the target population, the drug will provide clinically significant relief of the type claimed (21 CFR 330.14(a)(4)(ii)). Based on the available data concerning the harmful effects of UV radiation and sunscreen UV protection, we have concluded that sunscreens, in conjunction with the critical behavioral steps of limiting time in the sun particularly during the midday hours and wearing protective clothing (long sleeve shirt, pants, hat, and sunglasses), provide ''clinically significant relief'' in reducing the risk of skin cancer and early skin aging. Based on the available data, we have limited this claim to broad spectrum sunscreen products with an SPF value of 15 or higher.

UV radiation from the sun has been associated with nonmelanoma skin cancers since 1927 and with melanomas since 1952 (Ref. 13). It is estimated that as much as 90 percent of melanomas and nonmelanomas are caused by sun exposure (Ref. 5). In 1992, the International Agency for Research on Cancer (IARC), under the auspices of the World Health Organization, identified UV radiation as a human carcinogen [3] (Ref. 14). More recently, broad spectrum UV radiation was listed as a human carcinogen in the National Toxicology Program's 11th Report on Carcinogens issued in 2005 (Ref. 15). It is important to note that this report indicates that UVB and UVA radiation across the spectrum are known human carcinogens, but that either UVB radiation alone or UVA radiation alone is ''reasonably anticipated to be a human carcinogen.'' This classification is due to the fact that the exact wavelengths of UV radiation that cause different harmful effects (*e.g.,* DNA damage or loss of skin elasticity) have not yet been identified. It is clear, though, that broad spectrum UV radiation causes skin cancer. Broad spectrum UV radiation has also been shown to cause other types of skin damage, including early skin aging (Refs. 6 and 16). Therefore, we agree

[3] A carcinogen is anything that is known to cause the development of cancer. UV radiation is known to cause skin cancer.

with the principle that a reduction, of sufficient magnitude, in broad spectrum UV exposure should reduce the risk of harmful effects to the skin, including skin cancer and early skin aging.

Broad spectrum sunscreens, by absorbing UVA and UVB radiation, decrease consumer exposure to both types of UV radiation from the sun that reach the earth's surface. Other critical behavioral steps, such as limiting time in the sun and wearing protective clothing, also decrease consumer exposure to UVA and UVB radiation. After considering the submissions and other available data, we have concluded that a claim for the reduction in risk of skin cancer and early skin aging is appropriate for certain sunscreen products, when the claim also includes the requirement that consumers use the product as directed and the Directions specify other sun protection measures be followed (see section IV.D of this document). We are basing this claim on the scientific understanding of the harm from UVA and UVB radiation and the absorption and/or reflection of that UV radiation by broad spectrum sunscreens, as well as data from studies concerning sunscreen use and the development of skin cancer or precursors of skin cancer (section IV.B.2.c of this document).

For a sunscreen to be effective (*i.e.,* provide ''clinically significant relief'') in reducing the risk of skin cancer and early skin aging, consumers must not increase their overall exposure to UV radiation by overreliance on sunscreen use. Other behavioral factors could account for such an increase, such as the amount of time spent in the sun and the use of protective clothing. If consumers rely on sunscreen use to spend more time in the sun and/or to wear less protective clothing, then consumers could actually increase their overall UV exposure, which would eliminate the effectiveness of sunscreen use in reducing the risk of skin cancer and early skin aging.

To illustrate this point, it is helpful to consider what has been termed the ''compensation hypothesis.'' As we noted in the 2007 proposed rule, the compensation hypothesis states that consumers who wear high SPF sunscreens generally spend more time in the sun and/or wear less protective clothing (72 FR 49070 at 49086). If the hypothesis is true, consumers would not reduce their risk of skin cancer or early skin aging because their overall UV exposure increases, even though a properly applied (and reapplied) sunscreen absorbs UV radiation and helps prevent sunburn. We cited two retrospective studies which support the compensation hypothesis in the 2007 proposed rule (72 FR 49070 at 49086). Reynolds *et al.* published a study in 1996 finding, in a study of 509 sixth-graders, that adolescents who used sunscreen on both Saturday and Sunday of a Labor Day weekend spent significantly more time in the sun than those who used sunscreen only one day or not at all (Ref. 17). In the second study, parents of 503 children, aged less than 2 to 12 years, were surveyed as to parental attitudes about their children's sun exposure (Ref. 18). The authors reported that ''sunscreen use in children was significantly associated with longer duration of sun exposure'' (Ref. 18).

Increased overall UV exposure might, in fact, increase the risk of skin cancer and early skin aging, despite the proper use of sunscreens. Likewise, if consumers limit time in the sun, especially during midday, and wear more protective clothing (such as broad brimmed hats, long pants, and long sleeve shirts) while outside, but do not use sunscreens for areas of the skin exposed to the sun (such as parts of face and neck), then the consumer may not decrease the risk of skin cancer and early skin aging for sun-exposed areas. For these reasons, for products that are entitled to include an indication for reducing the risk of skin cancer and early skin aging, we continue to direct consumers to follow a comprehensive sun protection program that includes use of sunscreens with Broad Spectrum SPF values of 15 or higher, limiting time in the sun, and wearing protective clothing, similar to the sun protection measures discussed in the 2007 proposed rule (72 FR 49070 at 49089). Nearly identical multi-step behavioral sun protection programs are advocated by a number of medical and public health organizations, including the American Academy of Dermatology, the Skin Cancer Foundation, and the American Cancer Society.

We have concluded that a comprehensive sun protection approach is critical to ensure that consumers who are seeking to obtain a reduction in the risk of skin cancer and early skin aging limit their overall sun exposure. Without the reduction in consumers' overall UV exposure, even a sunscreen with Broad Spectrum SPF value of 15 or higher may not be effective in decreasing the risk of skin cancer and early skin aging. As discussed below, the available clinical studies do not control for these behavioral factors and, therefore, do not demonstrate that even this subset of sunscreens alone reduce the risk of skin cancer and early skin aging. However, based on the scientific understanding of the harm from UV exposure and our assessment of the study data, we have concluded that if consumers use sunscreens with Broad Spectrum SPF values of 15 or higher, limit time in the sun especially during the midday hours, and wear protective clothing when exposed to the sun, the resulting reduction in overall UV exposure will reduce the risk of skin cancer and early skin aging. Therefore, there is sufficient evidence of ''clinically significant relief'' to justify the indication and related directions for this subset of products, as set forth in the rule. However, we conclude that the omission of prominent information in the indication regarding the need for other sun protection measures would misbrand the product, as would the omission of the associated direction specifying these measures. Indeed, it would suggest a different indication than that which available evidence supports. Consequently, we have included in this final rule a new provision indicating that ''Any labeling or promotional materials that suggest or imply that the use, alone, of any sunscreen reduces the risk of or prevents skin cancer or early skin aging will cause the product to be misbranded under section 502 of the FD&C Act (21 U.S.C. 352).'' (new 21 CFR 201.327(c)(3)).

c. Available Scientific Data

We are not aware of any data other than what we reviewed in the 2007 proposed rule that evaluate the effectiveness of sunscreens in reducing the risk of skin cancer or early skin aging for healthy subjects. One more recent study, published in 2009, found that regular use of Broad Spectrum SPF 50+ sunscreen ''may prevent'' the development of actinic keratoses and non-melanoma skin cancer in immune-compromised organ transplant recipients (Ref. 19). We have not relied on this study in reaching our conclusions regarding OTC sunscreens, because we do not consider the immune-compromised study population to be representative of the general population.

We have re-evaluated the data originally reviewed in preparing the 2007 proposed rule to determine whether those data support allowing the indication for all sunscreen products or only for certain sunscreen products. Based on our re-evaluation, we have concluded that the data is supportive of an indication for broad spectrum sunscreens having SPF values of at least 15. Further, we have determined that, while the existing evidence does not support a claim for the use of any sunscreen alone, it does support an indication that the combination of using

a sunscreen with Broad Spectrum SPF value of 15 or higher along with other sun protection measures, reduces the risk of skin cancer and early skin aging, consistent with other positions in the 2007 proposed rule (72 FR 49070 at 49087 through 49090).

To date, there are no clinical studies demonstrating that use of any sunscreen alone can prevent skin cancer. There are two prospective [4] studies that directly examine the role of sunscreen products in preventing skin cancer. Although it did not show any difference in primary endpoints, a large 1999 study conducted in Australia demonstrated that people who applied a Broad Spectrum SPF 15 sunscreen product on a daily basis over a 4.5 year period had a lower overall incidence of one type of skin cancer, squamous cell carcinoma, on the head, neck, arms, and forearms than study participants who did not apply sunscreen (28 cases in the broad spectrum sunscreen group vs. 46 cases in the group not using broad spectrum sunscreen) (Ref. 20). In an extension of that study, van der Pols *et al.* evaluated the same population of subjects over an additional 8 years, and found that the sunscreen users continued to have a statistically significant lower incidence of squamous cell carcinoma over the entire 12.5 year period (Ref. 21). Neither study found that daily sunscreen use had any measurable effect on the most common form of skin cancer, basal cell carcinoma. Further, we are not aware of any studies examining the effect of sunscreen use on the development of melanoma, which is the deadliest form of skin cancer.

Although data from clinical studies addressing the specific end points of cancer is limited, some prospective studies have evaluated the effects of regular sunscreen use on the development of surrogate skin lesions that can be precursors to cancer: actinic keratoses and melanocytic nevi. A small percentage of actinic keratoses progress to squamous cell carcinomas (Ref. 22). At least four studies have demonstrated that the number of actinic keratoses is lower for individuals regularly using sunscreens with Broad Spectrum SPF values of 15 or higher (Refs. 23 through 26). We are not aware of any studies examining the potential effects on surrogate skin lesions of sunscreens that either are not broad spectrum or are broad spectrum with SPF values less than 15.

Two prospective studies have shown that regular use of a Broad Spectrum SPF 30 sunscreen reduces the risk of developing melanocytic nevi, which can progress into melanomas (Ref. 22). In a 2000 study, Gallagher *et al.* examined the formation of new melanocytic nevi in 393 Canadian school children. The group of children given Broad Spectrum SPF 30 sunscreen product had fewer new nevi over the course of the three year study than did children not given sunscreen products or advice on sunscreen use (Ref. 27). The difference was small (24 v. 28 nevi, respectively), but statistically significant ($p = 0.048$). In a follow-up study published in 2005, Lee *et al.* evaluated the same group of children for differences in melanocytic nevi by location on the body and demographic factors (Ref. 28). These investigators found that the sunscreen group had significantly fewer new nevi on the trunk than the control group ($p = 0.05$).

With respect to the role of sunscreen products in decreasing the risk of early skin aging, we are aware of only indirect evidence that sunscreen use decreases early skin aging. One recent study demonstrated that a broad spectrum sunscreen product can reduce the extent of solar UV-induced damage to factors associated with early skin aging even when the SPF value is less than 10 (Ref. 29). Although this study was small, evaluating only 12 Caucasian subjects, it shows the importance of broad spectrum protection. These findings have been corroborated in a large number of studies using broad spectrum sunscreens with SPF values ranging from 19 to 50, as reported by Fourtanier *et al.* in two recent reviews (Refs. 10 and 30).

Neither those studies evaluating the long term effect of regular sunscreen use on the development of skin cancer and early skin aging nor those evaluating the long term effect of sunscreen use on surrogate markers for these conditions were adequately controlled. Such studies, which must take place over many years, make adequate controls extremely difficult, if not impossible to implement. For example, one cannot control for time and duration of exposure, application and re-application amounts, or use of supplemental behavioral measures such as wearing protective clothing for a study which takes place over several years.

Despite their limitation, the results of the short-term effectiveness studies are consistent with our understanding that measures which significantly reduce UV exposure decrease the risk of skin cancer and early skin aging. UVA and UVB radiation is the only known external risk factor for skin cancer and early skin aging. Therefore, measures that significantly reduce both UVA and UVB exposure should decrease the risk of skin cancer and early skin aging. Based on this understanding, limiting time in the sun, wearing protective clothing and using a broad spectrum sunscreen with an SPF value of 15 or higher should decrease the risk of skin cancer and early skin aging. Using a broad spectrum sunscreen with an SPF value of 15 or higher ensures adequate breadth and magnitude of UVA and UVB protection. For these products, the broad spectrum test measures breadth and SPF test measures magnitude of UV protection. Consistent with this scientific principle, the short-term effectiveness studies demonstrate a decrease in the development of surrogates for skin cancer and early skin aging. Thus, we have concluded that the available evidence supports our finding that sunscreen products, in conjunction with limiting time in the sun and wearing protective clothing, reduce the risk of developing skin cancer or early skin aging.

d. Indication Limited to Covered Sunscreens With Broad Spectrum SPF Values of 15 or Higher

In light of the submissions requesting that we reframe our labeling information regarding sunscreen use and reduced risk of skin cancer and premature skin aging as an indication, we re-evaluated skin cancer and aging studies discussed in the 2007 proposed rule to determine whether the skin cancer and early skin aging indication should apply to all sunscreen products or be limited to certain sunscreen products. Available data support this indication only for broad spectrum sunscreens with SPF values of 15 or higher. Several reports have indicated that UV-induced skin damage associated with both skin cancer and early skin aging can be reduced by the use of broad spectrum sunscreens (Refs. 10 and 29 through 31). In a direct comparison of a broad spectrum sunscreen and a non-broad spectrum sunscreen with the same SPF, Moyal and Fourtanier found that the broad spectrum sunscreen provided significantly better protection from UV radiation-induced immunosuppression, a factor associated with both skin cancer and early skin aging (Ref. 32). Furthermore, the National Toxicology Program classified broad spectrum UV radiation as a known human carcinogen because it is not clear which UVB and/or UVA wavelengths contribute to the development of cancer (Ref. 15).

[4] A prospective study is designed to study subjects under pre-specified conditions. These studies differ from retrospective studies that try to prove hypotheses by assessing past experiences. Generally, prospective studies are superior to retrospective studies in demonstrating drug effectiveness.

Therefore, available data indicate that a broad spectrum sunscreen is necessary to reduce the risk of skin cancer. Likewise, we do not know which UVB and/or UVA wavelengths contribute to early skin aging. Therefore, it is reasonable to conclude that reducing the risk of early skin aging also requires a broad spectrum sunscreen (in conjunction with limiting time in the sun and wearing protective clothing).

With regard to SPF value, the available study data concerning the use of sunscreens in reducing the risk of skin cancer is based on products with SPF values of 15 or higher. The sunscreen product used in the 1999 Australian study on skin cancer (squamous cell and basal cell carcinomas) had a Broad Spectrum SPF value of 16, and those that were found to reduce actinic keratoses and nevi had SPF values ranging from 16 to 46. The studies on early skin aging make it difficult to know for certain whether Broad Spectrum SPF values of 15 or higher are necessary to reduce the risk of early skin aging. However, we conclude that the data regarding the minimum sunscreen protection necessary to reduce the risk of skin cancer can be extrapolated to early skin aging. In many ways, the biological processes that take place in response to UV radiation are similar for both conditions. For both skin cancer and early skin aging, UV radiation causes damage in the skin that is not completely repaired and leads to cancer, fine lines, wrinkles, etc. Because the supporting data for a skin cancer claim are based on products with SPF values of 15 or higher, we are only allowing the skin cancer and early skin aging claim for covered sunscreen products that are broad spectrum and have SPF values of at least 15. This rule does not preclude approval of a new drug application including an indication for reduction in risk of skin cancer and early skin aging for any sunscreen product. To be approved, such an application must be supported by the submission of adequate data. This rule also does not preclude future amendment of the sunscreen monograph in 21 CFR part 352, if additional data are provided to support a similar indication for other types of sunscreens.

e. Precedent for an Indication Statement That Includes Behavior Modification

There is at least one other OTC drug product with an indication statement that describes not only the drug's intended effect but also one or more behavioral measures to ensure the effect. The indication statement on the weight loss aid orlistat states that the product is to be used ''for weight loss in overweight adults, 18 years and older, when used along with a reduced-calorie and low-fat diet'' (Ref. 33). The behavioral measure of reduced caloric intake is necessary for consumers to experience weight loss. A low-fat diet is necessary for consumers to avoid the undesirable side effect of diarrhea caused by consuming a high-fat diet while taking orlistat.

The need to include reduced caloric intake as part of the indication statement for orlistat is similar to the need for including the use of other sun protection measures as part of the indication statement for sunscreens. Orlistat increases the likelihood of weight loss by preventing fat from being absorbed as food is digested in the stomach and intestines. If consumers take orlistat and decrease their caloric intake, they increase the likelihood of losing weight. However, if consumers increase their caloric intake while taking orlistat, they are less likely to lose weight. Orlistat's effect of preventing fat absorption could be offset by the high number of calories being eaten. Similarly, the reduction in UV exposure afforded by use of broad spectrum sunscreens with SPF values of 15 or higher can be offset if consumers increase their UV exposure by spending more time in the sun and/or wearing less protective clothing. This increased overall exposure could eliminate the effectiveness of sunscreen use in reducing the risk of skin cancer and early skin aging.

The labeling of prescription cholesterol-lowering drug products (*i.e.,* statins) follows a similar principle by emphasizing that reduction of cholesterol levels requires not only use of the drug product but also a healthy diet. The National Institutes of Health (NIH) specifies therapeutic lifestyle changes that can be followed to lower levels of cholesterol in the blood (Ref. 34). These changes include following a diet restricted in saturated fat and cholesterol, exercising regularly, and managing weight. Used in conjunction with cholesterol reducing drugs (currently available only by prescription), these lifestyle changes improve the chance of effectively treating high cholesterol levels.

Prescription cholesterol-lowering drug products include the behavioral step of following a low fat diet in the indication statement (Ref. 35). The body produces cholesterol, which the drug product inhibits to produce the desired drug effect of lowering cholesterol being made by the body. However, the total cholesterol circulating in the blood reflects cholesterol made by the body plus cholesterol absorbed from foods containing fats. Therefore, if consumers use a statin and minimize the amounts of food containing fats in their diet, then they will reduce the total cholesterol level in the blood. However, if consumers do not minimize the amounts of food containing fats in their diet, they may not reduce the total cholesterol in the blood. The decreased cholesterol production in the body caused by the statin may not be significant compared to the high amount of cholesterol derived from food eaten by consumers.

In the same way that regularly taking an OTC weight loss aid or a prescription cholesterol-lowering drug product without also following a healthy diet may not result in the intended health effect, use of a sunscreen with Broad Spectrum SPF value of 15 or higher without also limiting time in the sun and covering sun-exposed areas may not result in a net reduction in the risk of developing skin cancer or early skin aging. For this reason, we are requiring that the indication statement allowed on sunscreens with Broad Spectrum SPF values of 15 or higher include all parts of the sun protection program and not suggest or imply that use of a sunscreen alone reduces the risk of skin cancer or early skin aging.

C. Warnings

We received submissions requesting that we revise warnings included in the 2007 proposed rule and that we add new warnings not included in the 2007 proposed rule (Ref. 1). In section IV.C.1 of this document, we discuss one new and one revised warning included in this final rule. We are adding the new warning ''Do not use on damaged or broken skin'' (new 21 CFR 201.327(d)(1)). We are revising the warning about skin rash (proposed 21 CFR 352.52(c)(3)): ''Stop use and ask a doctor if skin rash occurs'' to read ''Stop use and ask a doctor if rash occurs.''

In section IV.C.2 of this document, we discuss our revision to the proposed ''Sun Alert'' warning. Under this final rule, the warning proposed for all monograph sunscreens is replaced with an optional indication and required direction on covered sunscreens with Broad Spectrum SPF values of 15 or higher, while covered sunscreens that are broad spectrum with SPF values less than 15 or that do not provide broad spectrum protection will bear a revised warning, called the ''Skin Cancer/Skin Aging Alert.'' (new 21 CFR 201.327(d)(2)).

In section IV.C.3 of this document, we discuss three new warnings that were requested in submissions, but are not

being included in this document. Submissions argued that we should add warnings that the regular use of sunscreen products may cause vitamin D deficiency and may reduce the photoprotective effects of tanning. We also considered adding a warning concerning sunscreen products containing alpha hydroxy acids (AHAs). We are not adding any of these warnings because the available data do not support the need for these warnings.

In summary, this document requires the following warnings on all covered OTC sunscreen products (new 21 CFR 201.327(d)):

- ''Do not use on damaged or broken skin''
- ''Stop use and ask a doctor if rash occurs''
- ''When using this product keep out of eyes. Rinse with water to remove.''

For all covered sunscreen products that either are not broad spectrum or are broad spectrum with SPF values less than 15, this final rule also requires a ''Skin Cancer/Skin Aging Alert'' as the first statement under the heading Warnings. In addition to these warnings, all sunscreen products are required to include the ''external use'' and ''keep out of reach of children'' warning statements required on all topical OTC drug products (21 CFR 201.66(c)(5)(i) and (c)(5)(x)).

1. New and Revised Warnings for Damaged or Broken Skin and Rash

The new warning that we are requiring on all covered sunscreen drug products reads, ''do not use on damaged or broken skin.'' We require this warning or a similar warning for other topical OTC drug products:

- Acne treatments (21 CFR 333.350(c)(3))
- Skin protectants (21 CFR 347.50(c)(6))
- Antiperspirants (21 CFR 350.50(c)(1))

The safety data for these ingredients are based on application to intact (*i.e.,* unbroken or undamaged) skin. We do not have data of the safe use of these ingredients if the skin is not intact. For the same reason, the warning appears on sunscreen products marketed under new drug applications (NDAs).[5] Therefore, in this document, we are requiring this warning for all covered OTC sunscreen products, which are marketed without approved applications (new 21 CFR 201.327(d)(1)(i)).

In addition to the new warning, we are revising the warning in proposed 21 CFR 352.52(c)(3): ''Stop use and ask a doctor if skin rash occurs.'' We are deleting the word ''skin'' so that the new warning reads: ''Stop use and ask a doctor if rash occurs'' (new 21 CFR 201.327(d)(1)(iii)). We received two submissions arguing that the word ''skin'' is unnecessary in this warning because every rash is a skin rash (Ref. 1). We agree and are removing the word to make the warning more concise. Consumers will likely understand the warning without the word ''skin.''

2. Revision of the Proposed ''Sun Alert'' Warning

In 2007, we proposed a warning, based on the ''Sun Alert'' statement cited in the 1999 stayed sunscreen final rule (64 FR 27666 at 27679), as the first statement under the heading Warnings for all monograph sunscreen products regardless of SPF value or broad spectrum protection (proposed 21 CFR 352.52(c)(1)). As proposed, this warning would have stated, ''UV exposure from the sun increases the risk of skin cancer, premature skin aging, and other skin damage. It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen.'' Submissions regarding this proposed warning are discussed in section IV.B.2 of this document. As noted there, we agree that, as proposed, this warning included an implied indication that all sunscreens reduce the risk of skin cancer and skin aging. Under this final rule, we are no longer requiring a ''Sun Alert'' or similar warning on broad spectrum sunscreens with SPF values of 15 or higher covered by the rule. This decision is based on our re-evaluation of the available scientific data. We are now permitting an indication stating that, used as directed with other sun protection measures, these sunscreens reduce the risk of skin cancer and premature skin aging (new 21 CFR 201.327 (c)(2)).

For these products we are also requiring a new direction statement (new 21 CFR 201.327(e)(1)(iv)). The direction states:

> Sun Protection Measures. [in bold font] Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a Broad Spectrum SPF of 15 or higher and other sun protection measures including: [bullet] limit time in the sun, especially from 10 a.m.–2 p.m. [bullet] wear long-sleeved shirts, pants, hats, and sunglasses

We have concluded that information about decreasing sun exposure and wearing protective clothing is more appropriate in ''Directions'' than in ''Warnings.'' These measures, in addition to use of a sunscreen with Broad Spectrum SPF value of 15 or higher, are necessary for the consumers' sun protection as part of a comprehensive program.

For covered sunscreen products that do not provide broad spectrum protection or those that do provide broad spectrum protection with SPF values less than 15, we conclude that a warning regarding the risks of skin cancer and skin aging remains necessary. In light of comments received on the ''Sun Alert'' warning proposed in 2007, however, we are revising the text to read as follows: ''Skin Cancer/Skin Aging Alert [in bold font]: Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, not [in bold font] skin cancer or early skin aging.'' (new 21 CFR 201.327(d)(2). The title ''Skin Cancer/Skin Aging Alert'' more accurately and specifically conveys the nature of the warning that follows than the proposed ''Sun Alert'' warning, particularly since the products that will bear this statement are indicated to help prevent sunburn, one consequence of sun exposure. The first sentence of this warning is a factual statement similar in content to the opening statement of the warning proposed in 2007. Like the proposed ''Sun Alert'' warning, this statement alerts consumers to risks they continue to incur from sun exposure, the conditions under which they will make use of the product. The second sentence clarifies for users the limits on the benefits that the product in hand has been established to provide, specifying that these products have been shown to help prevent sunburn but have not been shown to reduce the risk of skin cancer or early skin aging. Inclusion of this warning is critical to help ensure that consumers do not mistakenly conclude that all sunscreens have been demonstrated to provide the same benefits. It will reinforce the distinction between sunscreens indicated only for preventing sunburn (those that have broad spectrum with SPF values below 15 or that are not broad spectrum) and sunscreens that have also been shown to reduce the risk of skin cancer and early skin aging when used as directed with other sun protection measures (those with Broad Spectrum SPF values of 15 or higher). This warning serves a similar purpose to one required on cosmetic suntanning preparations that do not contain a sunscreen ingredient, which likewise is intended to assist consumers in distinguishing among products that they might otherwise confuse. (See 21 CFR 740.19).

[5] NDAs 21–501, 21–502, 21–471, and 22–009.

3. Warnings Requested in Submissions But Not Included in This Final Rule

We considered adding the following three warnings:

- Sunscreens may reduce the photoprotective effects of tanning
- Increased sun sensitivity caused by alpha hydroxy acids (AHAs) in sunscreen products
- Regular use of sunscreen products may cause vitamin D deficiency

However, as discussed in this section of the document, we conclude that these warnings are not needed for the safe and effective use of sunscreen products.

We received a submission arguing that we should require the following warning on all OTC sunscreen products containing UVA-protective active ingredients (Ref. 1): ''The use of this product will prevent the development of photo-protective facultative pigmentation, a.k.a., a tan.'' The submission implies that UVA protection is not only unnecessary but harmful to consumers. No data were included in the submission.

We agree that tanning caused by UVA radiation offers some protection against sunburn. However, tanning, particularly when attributable to prolonged exposure to UVA radiation in tanning beds or booths, may also have harmful effects on the skin (Refs. 36 and 37). In addition, one study suggests that the protective effects of tanning are small, as a tan only appears to provide an SPF value of approximately 4 (Ref. 36). As stated in the 2007 proposed rule (72 FR 49070 at 49083), we do not know which UVA wavelengths cause specific types of damage (*e.g.,* skin cancer or early skin aging). We continue to assert, however, that protection against UVA radiation is important for consumers' health (72 FR 49070 at 49083). We have concluded that the warning suggested in the submission is not in the best interest of public health because the warning discourages consumers from using broad spectrum sunscreen products. Therefore, we are not requiring any warning related to tanning.

We are not adding any additional warnings to sunscreen products containing AHAs. In the 2007 proposed rule, we requested comment on the need for additional warnings or directions on sunscreen products combined with AHAs (72 FR 49070 at 49110). We made this request in response to a 2005 guidance that we issued for cosmetic products containing alpha hydroxy acids (70 FR 1721, January 10, 2005). The guidance recommends the following warning be included on cosmetic products containing alpha hydroxy acids: ''Sunburn Alert: This product contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen and limit sun exposure while using this product and for a week afterwards.''

Many cosmetic products containing alpha hydroxy acids also contain sunscreens because the sunscreen helps protect the skin made sensitive to the sun by the alpha hydroxy acids. The guidance does not address products combining alpha hydroxy acids and sunscreens.

Two submissions stated that additional warnings are not necessary on these products (Ref. 1). We agree with these submissions. We considered added a warning or other labeling to inform consumers that AHAs contained in some sunscreen products may make the consumer more likely to sunburn. However, the sunscreen component of such products would, in fact, protect consumers from sunburn. Furthermore, we have concluded that the addition of sunscreen active ingredients to AHA-containing cosmetic products provides valuable UV protection for consumers. Therefore, at this time, we have concluded that a warning about AHA is not necessary on OTC sunscreen products.

The other new warning requested in submissions relates to vitamin D deficiency. We received six submissions arguing that consumers should be warned that frequent sunscreen use may result in vitamin D deficiency (Ref. 1). The submissions cite articles discussing the negative effects of vitamin D deficiency, such as growth retardation, rickets, and osteoporosis (Ref. 38). The submissions include numerous published articles concerning vitamin D, but only four clinical studies that directly examine the effect of sunscreen use on vitamin D levels. In the remainder of this section, we discuss the four studies included in submissions, as well as three additional studies that we located through a literature search. Collectively, the studies do not demonstrate that the use of sunscreen causes vitamin D deficiency.

The term ''vitamin D'' refers to several forms of the vitamin, but the two forms important to humans are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) (Ref. 39). Vitamin D_2 is obtained by eating vitamin D-rich foods such as fish or food fortified with vitamin D. The skin makes vitamin D_3 when it is exposed to sunlight (Ref. 40) and, therefore, vitamin D production may vary depending on the following factors: (1) Skin pigmentation, (2) age, (3) clothing, (4) season, (5) latitude, (6) time of day, (7) weather conditions, and (8) sunscreen application (Refs. 40–43). Vitamin D deficiency has long been associated with Ricketts, but recent research suggests that vitamin D deficiency may also be associated with other diseases (Ref. 38). However, the threshold of vitamin D blood levels that constitutes a deficiency is currently being re-evaluated by scientific experts (Refs. 40, 44, and 45).

To determine whether sunscreen use causes vitamin D deficiency, we reviewed four clinical studies included in the submissions that explored the effect of sunscreen use on vitamin D levels as well as three studies that we identified in a literature search:

- Matsuoka *et al* 1987 (Ref. 46)
- Matsuoka *et al* 1988 (Ref. 47)
- Marks *et al.* 1995 (Ref. 48)
- Farrerons *et al.* 1998 (Ref. 49)
- Kimlin *et al.,* 2007 (Ref. 50)
- Cusack *et al.,* 2008 (ref. 51)
- Hoesl *et al.,* 2010 (Ref. 52).

All but one of these studies assessed 25-hydroxyvitamin D levels because 25-hydroxyvitamin D is typically used as the biological marker for vitamin D (in the D_2 or D_3 form) (Ref. 53). Much of the data available in the literature involves nonclinical studies, which can be difficult to extrapolate to consumer (human) actual use conditions. Studies with clinical data provide more meaningful results because, if adequately designed, they can be more easily extrapolated to consumer actual use conditions. Therefore, we are focusing discussion in this document on the clinical studies.

In the 1987 study by Matsuoka *et al.,* four subjects applied a sunscreen product with an unknown SPF to the entire body, while four control subjects did not apply any topical product (Ref. 46). All of the subjects were exposed to 1 MED[6] of UV radiation (260–330 nm[7]) and then vitamin D_3 levels were monitored for 15 days. The subjects using sunscreen product applied the sunscreen product 1 hour before UV exposure. The level of vitamin D_3 was determined one day before UV exposure to serve as the baseline measure.

The level of vitamin D_3 in the control group (no sunscreen) increased significantly over baseline 1 day after UV exposure (from ~2 ng/ml[8] to 25 ng/ml) and then decreased gradually, returning to baseline 15 days after UV exposure. In contrast, the levels of vitamin D_3 in the sunscreen group did

[6] MED refers to the lowest dose of UV radiation that produces perceptible reddening of the skin.

[7] Nanometers.

[8] Nanograms per milliliter.

not change significantly from the baseline level (5 ng/ml) at each time point.

Based on this preliminary study, Matsuoka *et al.* conducted another study in 1988 (Ref. 47). This study enrolled 40 subjects from Illinois and Pennsylvania with 20 subjects in the control group and 20 subjects in the sunscreen group. Each time they went outdoors for 1 year, the subjects in the sunscreen group, who had a history of skin cancer, applied a sunscreen product with an unknown SPF to all sun-exposed areas of the body.

Serum 25-hydroxyvitamin D levels were measured in each group at the conclusion of the study and were significantly lower in the sunscreen group than the control group: 40.2 and 91.3 nmol/L,[9] respectively. The difference in 25-hydroxyvitamin D levels between the two groups was statistically significant ($p < 0.001$).

Marks *et al.* conducted a randomized, double-blind controlled clinical study over a summer period in Australia (Ref. 48). In this study, 113 subjects over 40 years old who exhibited at least one solar keratosis (a precursor of carcinoma of the skin) were recruited and divided into two groups. The first group of 56 subjects applied an SPF 17 sunscreen cream. Fifty-five subjects in the control group applied a placebo cream. Subjects in both groups were asked to apply their cream on the head, neck, forearm and dorsal side of each hand once a day in the morning and more frequently if sweating, swimming, or involved in activities that might rub off the cream.

The mean levels of 25-hydroxyvitamin D rose significantly by almost the same amount in both groups over the period of the study. The mean level in the placebo group increased by 12.8 mmol/L, whereas the mean level in the sunscreen group increased by 11.8 mmol/L. The difference between these increases from baseline values was not statistically significant.

In 1998, Farrerons *et al.* carried out a study to examine the effects of sunscreen use on vitamin D levels in elderly individuals (Ref. 49). In this 2-year study, 24 subjects (10 men and 14 women with a mean age of 71 years) were enrolled in the sunscreen group. The subjects had actinic keratosis, basal cell carcinoma, or squamous cell carcinoma. None of the subjects had previously used sunscreen products, but were instructed to apply an SPF 15 sunscreen product to sun-exposed areas of the body each morning, avoid mid-day sun, and wear UV-protective clothing during the spring and autumn. The control group of 19 subjects did not use sunscreen product, but had the same skin characteristics. Mean serum levels of 25-hydroxyvitamin D were measured at eight different time points (four in the autumn and four in the spring) over the two-year study period.

The mean serum levels of 25-hydroxyvitamin D were statistically lower in the sunscreen group as compared to the control group at one spring and one autumn time point ($p < 0.05$). However, the mean serum levels of 25-hydroxyvitamin D were not statistically different between the groups at the other 6 spring and autumn time points.

In 2007, Kimlin *et al.* reported that there was ''no association'' between use of sunscreens with SPF values higher than 15 and blood levels of 25-hydroxyvitamin D in a study of 126 Australian adults 18–87 years of age (Ref. 50). However, the authors stated that mean levels of 25-hydroxy vitamin D increased with increasing frequency of sunscreen use. Interestingly, study ''participants who 'usually' or 'almost always' wore a hat when outdoors'' were significantly more likely to have higher serum 25-hydroxy vitamin D levels than those who wore hats less often (Ref. 50). On the other hand, study participants who usually or almost always wore long sleeve shirts or pants while outside were statistically more likely to have lower serum 25-hydroxyvitamin D levels than those who wore these types of protective clothing less often (Ref. 50).

In 2008, Cusack *et al.* reported that decreased levels of 25-hydroxyvitamin D levels were only ''weakly correlated'' with sunscreen usage in 52 Irish patients with cutaneous lupus erythematosus (Ref. 51). This study population was specifically selected because patients with lupus are particularly sensitive to exposure to the sun. While an analysis of the effects of daily sunscreen use on serum levels of 25-hydroxyvitamin D showed the relationship between these two parameters to be significant, a multivariate analysis of the same data was not significant (Ref. 51).

Most recently, in 2010, Hoesl *et al.* reported ''no statistically significant association'' between serum levels of 25-hydroxyvitamin D and use of the sunscreen drometrizole trisiloxane in a cohort of 15 patients with Xeroderma pigmentosum (Ref. 52). Like those with lupus ertythematosus, patients with Xeroderma pigmentosum are extremely sensitive to the sun. The authors reported that reductions in serum levels of 25-hydroxyvitamin D are ''not associated with any type or duration of sun protection applied by these patients'' (Ref. 52).

These seven clinical studies are inconclusive because the results were contradictory. Two studies suggest that sunscreens decrease vitamin D levels and the other five studies suggest that sunscreens do not decrease vitamin D levels. In addition, the studies were relatively small, only enrolling 8 to 126 subjects. The study with the greatest number of participants was inconclusive showing that people who regularly used sunscreens and wore hats had increased levels of vitamin D, whereas people who regularly wore pants outside had decreased levels (Ref. 50).

Because the preponderance of currently available data suggests that sunscreen use does not cause clinically meaningful decreases in vitamin D levels (*i.e.,* decreases that lead to vitamin D deficiency and/or disease caused by low levels of vitamin D), we are not including a warning regarding vitamin D deficiency on OTC sunscreen products. In addition, determining whether decreases in vitamin D levels result in vitamin D deficiency is especially difficult because the threshold of vitamin D blood levels that constitutes a deficiency is currently being re-evaluated by scientific experts (Refs. 38, 44, and 45). We recognize that certain subpopulations may be at increased risk of vitamin D deficiency, as pointed out in one submission. However, there are many factors that determine the amount of sun exposure necessary to ensure adequate vitamin D levels (*e.g.,* geographical location, season, skin pigmentation, dietary vitamin D intake). Because of these many other factors, it is difficult for us to determine a meaningful message in sunscreen product labeling for consumers, especially in the absence of conclusive data. If we become aware of data from adequate and well-controlled studies demonstrating that regular use of sunscreen causes vitamin D deficiency, we will re-evaluate this issue.

D. Directions

We received numerous submissions requesting that we revise directions included in the 2007 proposed rule (Ref. 1). In response to those requests and our reevaluation of OTC sunscreen labeling, we are revising the following directions:

- ''Reapply after [select one of the following: '40 minutes of' or '80 minutes of' '' for products that satisfy either the water resistant or very water resistant test procedures in proposed paragraphs 352.76(a) and (b), respectively] swimming or [select one of the

[9] Nanomoles per liter.

following: 'sweating' or 'perspiring'] and after towel drying. Otherwise, reapply at least every 2 hours'' (proposed 21 CFR 352.52(d)(2)).

- ''Reapply at least every 2 hours after towel drying, swimming, or sweating'' (proposed 21 CFR 352.52(d)(3)).

These two directions are the reapplication instructions for water resistant and non-water resistant products, respectively. We also received five submissions requesting that we revise the direction: ''Apply [select one of the following: 'liberally' or 'generously'] [and, as an option: 'and evenly'] [insert appropriate time interval, if a waiting period is needed] before sun exposure'' (proposed 21 CFR 352.52(d)(1)(i)). As discussed in this section, we are not revising this direction statement.

In addition to the revisions to these provisions (described in more detail in this section of the document), we are no longer requiring the following proposed direction: ''Apply and reapply as directed to avoid lowering protection'' (proposed 21 CFR 352.52(d)(1)(ii)).

As already discussed, for covered sunscreen products with Broad Spectrum SPF values of 15 or higher, we are requiring the following direction:

''Sun Protection Measures. [in bold font] Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a Broad Spectrum SPF of 15 or higher and other sun protection measures including: [bullet] limit time in the sun, especially from 10 a.m.–2 p.m. [bullet] wear long-sleeved shirts, pants, hats, and sunglasses''

(new 21 CFR 201.327(e)(1)(iv)). For these products, this direction most appropriately conveys the information proposed in the ''Sun Alert'' warning included in the 2007 proposed rule, and provides the necessary directions to complement the new indication permitted for these products.

In addition to the required directions, we will allow the optional direction heading ''for sunscreen use'' (new 21 CFR 201.327(e)(1)(i)).

1. Revised Directions

We are revising the directions for water resistant sunscreen products (new 21 CFR 201.327(e)(2)) to read:

- Reapply:
- After 40 [or 80] minutes of swimming or sweating
- Immediately after towel drying
- At least every 2 hours

We are also revising the directions for non-water resistant sunscreen products (new 21 CFR 201.327(e)(3)) to read: ''[Bullet] reapply at least every 2 hours [bullet] use a water resistant sunscreen if swimming or sweating.'' These revisions should clarify the directions. We are removing reapplication directions concerning swimming and sweating from non-water resistant products because these products should not be used when swimming or sweating. Instead, we are requiring more accurate directions instructing consumers to use a different sunscreen product—a water resistant sunscreen product—if swimming or sweating.

We considered revising the 2-hour reapplication timeframe because some of the submissions objected to this specific timeframe (Ref. 1). The submissions argued that we should require the word ''often'' instead of a 2-hour reapplication timeframe because there are no data supporting this timeframe. The submissions also point out that the American Academy of Dermatology (AAD) no longer supports a 2-hour timeframe, even though we cited AAD as supporting the 2-hour timeframe in the 2007 proposed rule (72 FR 49070 at 49093).

In its submission following the 2007 proposed rule, the AAD does not state its support for the 2-hour timeframe. However, all of the public education materials from AAD instruct consumers to reapply sunscreen at least every 2 hours (Refs. 54 through 58). In addition, other public health organizations such as the Centers for Disease Control and Prevention (CDC) and the U.S. Environmental Protection Agency (EPA) recommend reapplication at least every 2 hours (Refs. 59 and 60).

We disagree with the submissions stating that data do not support this timeframe. In the 2007 proposed rule, we described two studies demonstrating a significantly decreased sunburn risk if sunscreen product were applied at least every 2 hours (72 FR 49070 at 49092 through 49093). Wright *et al.* found that subjects who reapplied sunscreen every 1 to 2 hours and after swimming were not sunburned (Ref. 61). Similarly, Rigel *et al.* reported that people who reapplied sunscreen every two hours or sooner were five times less likely to sunburn compared to those who reapplied sunscreen only after 2.5 hours or longer (Ref. 62).

One of the submissions following the 2007 proposed rule included results from a computer-simulation of sunscreen product reapplication based on a mathematical model (Ref. 1). The results of this simulation suggested that sunscreen products should be reapplied 15 to 30 minutes after sun exposure begins. The results also suggested that further reapplication of sunscreen product is necessary after vigorous activity that could remove sunscreen product, such as swimming, toweling, excessive sweating, or rubbing. No other reapplication time is suggested. The usefulness of this study in determining whether to revise the directions is limited. In particular, we do not know whether this simulation was validated, because it has not been confirmed with clinical studies. Until we receive clinical studies demonstrating that consumers do not experience skin damage when sunscreen is reapplied at longer timeframes, we will continue to require the 2-hour reapplication timeframe. As discussed in the 1999 final rule, manufacturers may seek approval of different reapplication directions by submitting specific and substantive supporting data to us under an NDA deviation (described in 21 CFR 330.11).

2. Proposed Directions Not Being Revised

We are not revising proposed 21 CFR 352.52(d)(1)(i): ''Apply [select one of the following: 'Liberally' or 'generously'] [and, as an option: 'And evenly'] [insert appropriate time interval, if a waiting period is needed] before sun exposure.'' Several submissions requested that we allow ''smoothly'' to be included in this statement (Ref. 1). However, we continue to consider this word to be vague (72 FR 49070 at 49072 and 49092). Some submissions also requested that we include a specific application amount in place of the terms ''generously'' and ''liberally'' (Ref. 1). For example, the submissions suggested that the statement could read ''apply 2 tablespoonsful.'' The submissions argued that more specific directions would lead to consumers applying more sunscreen product, reflecting the 2 milligrams per square centimeter (mg/cm^2) used during the SPF test. However, specifying a certain amount in the directions will not accomplish this goal. The amount of sunscreen product that needs to be applied to reach 2 mg/cm^2 varies for each sunscreen product and depends on the amount of skin surface area being covered. For example, the volume of sunscreen oil applied to the neck and face will differ greatly from the amount needed to apply a sunscreen lotion to every sun-exposed area of the body. Therefore, we are continuing to require the terms ''generously'' and ''liberally.''

3. Proposed Directions Not Being Required

We are not requiring the proposed statement ''apply and reapply as directed to avoid lowering protection'' (proposed 21 CFR 352.52(d)(1)(ii)). We included this statement in the 2007

proposed rule because reapplication time appears to be critical to achieve proper sun protection (72 FR 49070 at 49093). However, we have concluded that this statement is redundant with more specific reapplication directions and may confuse consumers. It is not clear that consumers will understand the intent of this statement to emphasize the need to follow reapplication instructions. Therefore, we are not requiring the statement in this document.

4. New Directions Resulting From Submissions on the Proposed Rule

For covered sunscreens with Broad Spectrum SPF values of 15 or higher, we are requiring a new Directions statement that emphasizes the need not only to regularly use such a sunscreen, but also to follow other sun protection measures. For these sunscreens, the statement will read, ''[bullet] Sun Protection Measures. [in bold font] Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a Broad Spectrum SPF of 15 or higher and other sun protection measures including: [Bullet] limit time in the sun, especially from 10 a.m.–2 p.m. [bullet] wear long-sleeved shirts, pants, hats, and sunglasses (new 21 CFR 201.327(e)(1)(iv)). This statement is taken from the proposed warning ''UV exposure from the sun increases the risk of skin cancer, premature skin aging, and other skin damage. It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen.'' (proposed 21 CFR 352.52(c)(1)). As discussed in section IV.C. of this document, this warning is no longer being required for sunscreens with Broad Spectrum SPF values of 15 or higher. Rather, as discussed in section IV.B of this document, submissions suggested that the information proposed as a warning is better understood as an indication, with the supporting conditions for achieving effectiveness. As described in section IV.B, on reexamination of the scientific data, we agree that an appropriately limited indication for reduction in risk of skin cancer and early skin aging is supported for sunscreens with Broad Spectrum SPF values of 15 or higher. For these products, the direction instructs users how to use the product in a manner that supports that indication.

In this final rule, we are being more specific about the need to limit time in the sun especially during the midday hours of 10 a.m. to 2 p.m. when the intensity of solar radiation is greatest because the sun is at its zenith (*i.e.,* directly overhead). In our 1993 proposed rule, we stated that, ''on any day of the year, the intensity of the UV energy of sunlight is greatest between 10 a.m. and 2 p.m.'' (58 FR 28194 at 28199). We have concluded that this information is important to consumers trying to protect themselves from the sun and are including the information in the new direction statement. This change is also responsive to the concerns of two submissions on the portion of the proposed sun alert that referred to ''limiting time in the sun,'' both of which suggested alternatives intended to provide more concrete information for consumers to act on (Ref. 1).

Several submissions argued that we should allow different Drug Facts labeling for cosmetics containing sunscreens so that consumers will apply the product appropriately for its intended cosmetic use (Ref. 1). For example, the submissions argued that reapplication every 2 hours may not be appropriate for cosmetic-sunscreen products. We disagree with these submissions. Cosmetic-sunscreen combinations that are intended for use as drugs require adequate labeling for their drug use. (See 21 CFR 700.35). The Drug Facts label communicates information to the consumer so that the cosmetic-sunscreen product can be used safely and effectively. To help consumers understand that the sunscreen directions apply to the use of the product as a drug, for sun protection, we are allowing the optional statement ''for sunscreen use:'' to appear as the first line under ''Directions.'' Consumers who are using these products primarily for cosmetic use will be more likely to understand that they might not receive the intended sun protection if they do not follow the directions in the Drug Facts label.

E. Constitutionality of Labeling Statements Regarding Skin Cancer and Skin Aging

Two submissions questioned the constitutionality of the labeling provisions in the 2007 sunscreen proposed rule. Specifically, the submissions contended that our proposed restriction on any claims about the prevention of skin cancer, early skin aging, and related skin damage would violate the sunscreen manufacturers' commercial speech rights under the First Amendment to the U.S. Constitution.

In the 2007 proposed rule preamble, we had concluded that our proposed restriction on claims about the prevention of skin cancer, early skin aging, and related skin damage would be permissible under the First Amendment, in part, because, at that time, we tentatively concluded that there were insufficient scientific data to support inclusion of such claims in the sunscreen monograph. As described elsewhere in this document, we received numerous submissions in response to the 2007 proposed rule, some of which contained references to clinical studies we had reviewed in preparing the 2007 proposed rule about the effectiveness of sunscreens in protecting against the harmful effects of UV radiation. As already described in section IV.B.2, based in part on our re-evaluation of the data from these studies, as well as the scientific fact that reducing exposure to both UVB and UVA radiation by a substantial amount (*i.e.,* equivalent to that provided by a broad spectrum sunscreen with an SPF value of 15 or higher) decreases the risk of damaging the skin, we find that the science supports the conclusion that one subset of sunscreens covered by this rule, broad spectrum sunscreen products with an SPF value of 15 or higher, in conjunction with limiting time in the sun and wearing protective clothing, reduce the risk of developing skin cancer and early skin aging. Our conclusion is reflected in the permissible indication described in this final rule for covered products with Broad Spectrum SPF values of 15 or higher. Although we have decided to permit a claim about the prevention of skin cancer and early skin aging for certain covered sunscreens, as requested in the submissions, we have nevertheless conducted a First Amendment analysis of our requirements concerning the skin cancer/early skin aging claim in this final rule (hereinafter ''skin cancer/early aging indication''), as well as the ''Skin Cancer/Skin Aging Alert'' required as a warning for covered products that do not provide broad spectrum protection with an SPF value of 15 or higher. For the following reasons, we have concluded that these requirements do not violate the First Amendment.

This rule establishes effectiveness testing methods and labeling that are appropriate for the safe and effective use of OTC sunscreen products covered by this rule. Any covered sunscreen product that deviates from the requirements set forth in this labeling regulation and any other applicable labeling regulation would be considered misbranded under section 502 of the FD&C Act. In particular, sunscreen products covered by this rule would be misbranded if they are labeled with a skin cancer/early aging indication but

do not provide broad spectrum protection with an SPF value of 15 or higher. Such products would also be misbranded if they do not include the ''Skin Cancer/Skin Aging Alert'' described in this rule (see 21 CFR 201.327(d)(2)). Covered sunscreen products that do provide broad spectrum protection with an SPF value of 15 or higher would be misbranded if they are labeled with the permissible skin cancer/early aging indication but do not include reference to the need to use the product as directed with other sun protection measures (21 CFR 201.327(c)(3)). Manufacturers of covered sunscreen products that comply with the labeling requirements in this document would not be subject to enforcement actions on the basis that the products are misbranded, provided they comply with all other requirements under section 502 of the FD&C Act. Because this rule applies only to products marketed without approved applications, manufacturers who wish to deviate from the testing or labeling requirements in this document may do so by means of a new drug application (NDA) under section 505 of the FD&C Act.

We have concluded that the labeling requirements in this rule satisfy the applicable tests governing commercial speech, as set forth by the Supreme Court. The requirements for the ''Skin Cancer/Skin Aging Alert'' and the information in the skin cancer/early aging indication about using the product as directed with other sun protection measures, are permissible under the First Amendment because they are reasonably related to the Government's interest in protecting public health (see *Zauderer* v. *Office of Disciplinary Counsel,* 471, U.S. 626, 651 (1985)).

We are requiring covered sunscreen products that do not provide broad spectrum protection with an SPF value of 15 or higher to include the ''Skin Cancer/Skin Aging Alert'' under the ''Warnings'' heading on the label to ensure that consumers are aware of the continued risks of skin cancer and early skin aging that occur from sun exposure, the conditions under which they will be using the product, and that they understand that the product has been shown only to help protect against sunburn. Without this warning, consumers could fail to distinguish between these sunscreen products and other sunscreen products that have been proven to help provide protection against skin cancer and early skin aging. Providing this information is important for consumers to be able to make informed choices about the selection and use of sunscreens.

For covered sunscreen products that do provide broad spectrum protection with an SPF value of 15 or higher, we are requiring that the additional information about using the product as directed with other sun protection measures be included in the indication so that consumers are not misled about how to use these sunscreens effectively or about the conditions under which these sunscreens are effective. Use of a sunscreen alone—even a broad spectrum sunscreen with an SPF value of 15 or higher—has not been shown to reduce the risk of skin cancer or early skin aging if a consumer increases overall UV exposure by spending greater time in the sun and/or wearing less protective clothing. The additional information required in the skin cancer/early aging indication about using the product as directed with additional sun protection measures clarifies how the use of sunscreens is part of a comprehensive sun protection program. Displaying this information elsewhere would underemphasize its importance in relation to the use of these sunscreens for protection against skin cancer and early skin aging (see *N.Y. State Rest. Ass'n* v. *N.Y. City Bd. of Health,* 556 F.3d 114 (2d Cir. 2009); see also 21 U.S.C. 352(c)). Thus, these disclosure requirements will promote the proper use of covered sunscreens and are, therefore, reasonably related to the Government's interest in protecting public health.

Our requirements concerning the skin cancer/early aging indication would also be permissible under the First Amendment using the analytical framework provided in *Central Hudson Gas & Electric Corporation* v. *Public Service Commission,* 447 U.S. 557 (1980). Under *Central Hudson,* commercial speech that is false, misleading, or concerns unlawful activity is not entitled to protection under the First Amendment. While commercial speech that concerns lawful activity and is not misleading receives some protection under the First Amendment, it may nonetheless be regulated by the Government if the following conditions are met: (1) The asserted governmental interest is substantial; (2) the regulation directly advances the asserted governmental interest; and (3) the regulation is not more restrictive than necessary to serve that interest (*Id.* at 566). The Supreme Court has explained that the last element of the *Central Hudson* test is not a ''least restrictive means'' requirement but, rather, requires narrow tailoring (*i.e.,* ''a fit that is not necessarily perfect, but reasonable'' between means and ends) (*Board of Trustees of the State Univ. of N.Y.* v. *Fox,* 492 U.S. 469, 480 (1989)). In subsequent decisions, the Court has also clarified that ''misleading'' in the first element of the test refers to speech that is inherently or actually misleading.

Based on the data currently available, we have concluded that the following statements or omissions would be false or inherently misleading: (1) Use of the skin cancer/early aging indication on the labeling of a sunscreen product that does not provide broad spectrum protection with an SPF value of 15 or higher, (2) the omission of the ''Skin Cancer/Skin Aging Alert'' under the ''Warnings'' heading of the labeling for sunscreen products that do not provide broad spectrum protection with an SPF value of 15 or higher, and (3) use of the skin cancer/early aging indication that omits the required information about using the product as directed with other sun protection measures.

Use of the skin cancer/premature aging indication on the labeling of covered sunscreen products that do not provide broad spectrum protection with an SPF value of 15 or higher would be false or inherently misleading for several reasons. As discussed elsewhere in this document, only broad spectrum UV radiation is classified as a known human carcinogen, according to the National Toxicology Program. Therefore, covered sunscreen products that do not provide broad spectrum UV protection may not reduce the risk of skin cancer. Furthermore, since the precise wavelengths of UV radiation that cause skin cancer and early skin aging are unknown, a covered sunscreen product that only provides protection against part of the UV spectrum may not ensure a reduction in the risk of developing skin cancer or early skin aging. In addition, all of the scientific data that support the skin cancer/early aging indication for certain covered sunscreens were derived from studies that used sunscreen products with an SPF value of 15 or higher. Therefore, the skin cancer/early aging indication would be false or inherently misleading on covered sunscreen products that do not provide this level of protection, because there is a lack of any evidence demonstrating that these products would reduce the risk of skin cancer or early skin aging. Similarly, omitting the ''Skin Cancer/Skin Aging Alert'' on these products, which are identified on their labels as ''sunscreens,'' would be inherently misleading because consumers who are using these products for sun protection would not be sufficiently alerted to the fact that these products have been shown only to

protect against sunburn, while sun exposure also increases the risks of skin cancer and early skin aging.

A skin cancer/early aging indication on a covered product with Broad Spectrum SPF value of 15 or higher that omits the required information about using the product as directed with other sun protection measures would also be false or inherently misleading because sunscreen use alone has not been shown to reduce the risk of skin cancer or early skin aging if a consumer increases overall UV exposure by spending greater time in the sun and/or wearing less protective clothing. As discussed above in this section and elsewhere in this document, without the reduction in consumers' overall UV exposure, a covered sunscreen product may not be effective in reducing consumers' risk of skin cancer and early skin aging.

We also conclude that the labeling claims and omissions described above would cause the product to be misbranded and, therefore, relate to an unlawful activity. As described earlier in this section and elsewhere in this document, labeling regulations establish certain requirements that help ensure the safe and effective use of OTC drug products. The false or misleading labeling described above would cause covered products to be misbranded under section 502 of the act. Therefore, such labeling would concern the illegal sale of misbranded drugs. Under the *Central Hudson* test, then, we have not violated the First Amendment with these requirements, which simply prohibit false or inherently misleading labeling.

Although we conclude that the labeling described above would not be entitled to First Amendment protection under the threshold inquiry of the *Central Hudson* test, we conclude that our regulation directly advances a substantial Government interest and is no more extensive than necessary, and therefore would also pass muster under the test's three remaining steps. Under the first remaining step, we have a substantial interest in protecting public health (see *Pearson* v. *Shalala,* 164 F.3d 650, 656 (DC Cir. 1999) (citing *Rubin* v. *Coors Brewing Co.,* 514 U.S. 476, 484–485 (1995)).

Under the second remaining step of the *Central Hudson* test, our labeling requirements discussed in this section directly advance the Government's interests in protecting public health because they help ensure that covered sunscreen products are adequately labeled for safe and effective use by consumers.

As stated previously in this document, scientific evidence only supports the skin cancer/premature aging indication for sunscreen products that provide broad spectrum protection with an SPF value of 15 or higher. Allowing the skin cancer/early aging indication on sunscreen products for which it is not scientifically supported would lead to consumers unjustifiably relying on such products for protection against skin cancer and early skin aging. Furthermore, the ''Skin Cancer/Skin Aging Alert'' allows consumers to be aware that spending time in the sun increases their risk of skin cancer and early skin aging, and that products on which this alert appears have not been shown to provide this type of protection. The requirement for information in the skin cancer/early aging indication about using sunscreens as directed with sun protection measures also directly advances our interest in protecting public health because these elements are essential for consumers to reduce their overall UV exposure and, consequently, their risk of developing skin cancer and early skin aging. Thus, these requirements directly advance the Government's interest in protecting public health through the safe and effective use of sunscreens.

Under the final remaining step of the *Central Hudson* test, our requirements concerning the skin cancer/early aging indication are not more restrictive than necessary, because there are not numerous and obvious alternatives (*Cincinnati* v. *Discovery Network,* 507 U.S. 410, 418 n. 13 (1993)) to achieve the Government's substantial interests. By permitting the skin cancer/early aging indication only for covered sunscreen products with Broad Spectrum SPF values of 15 or higher, and requiring the ''Skin Cancer/Skin Aging Alert'' for products that do not offer this level of protection, we are ensuring that consumers do not mistakenly rely on sunscreen products that have not been demonstrated to be effective for protection against skin cancer and early skin aging. In addition, labeling that omits a statement regarding the use of other sun protection measures as directed from the skin cancer/early aging indication could lead to consumers foregoing other sun protection measures, thereby negating the protective effect of the sunscreen. Including a statement in the skin cancer/early aging indication regarding the need to follow other sun protection measures as well as the related directions ensures that consumers understand how to use sunscreens to reduce their risk of skin cancer and early skin aging.

It is important to note that manufacturers of OTC sunscreens covered by this rule have several alternatives for adding labeling information that is not included in this labeling regulation. For example, such manufacturers can file an NDA under section 505 of the FD&C Act or submit a petition under 21 CFR 10.30 to amend the labeling regulation. In either case, the manufacturer need only submit the requisite evidence to support the indication or other labeling for the product that differs from that addressed by the regulation. Therefore, we are not being more restrictive than necessary when these viable alternatives are available for manufacturers.

Reacting to the fact that our proposed rule did not permit any indication statement for any sunscreen regarding prevention of skin cancer and early skin aging, one submission asserted that we must consider use of a disclaimer as an alternative means of addressing the limits of the product's effectiveness. As noted previously in this document, this final labeling regulation permits an appropriately limited indication for broad spectrum sunscreens with SPF values of 15 or higher—one stating that when used as directed with other sun protection measures, such products decrease the risk of skin cancer and early skin aging caused by the sun. The claim is authorized for this subset of covered sunscreen products because available scientific data discussed elsewhere in this document are sufficient to substantiate the claim for these products. Because we have included a skin cancer/early skin aging claim in these labeling regulations, we no longer view the submission's request as being applicable.

In any event, we note that the use of disclaimers on drug labeling to qualify inadequately supported or unapproved indications is not an effective, less restrictive means of achieving FDA's substantial interests in protecting public health and preserving the integrity of its premarket approval systems. Indeed, disclaimers on drug labeling would severely undermine the Government's interests here. For over 100 years, Congress has charged FDA with enforcing misbranding laws to protect public health. In 1962, Congress amended the FD&C Act to require that all new drugs be approved as both safe and effective prior to marketing. Congress found that a premarket approval system, requiring specific types of supporting evidence (see 21 U.S.C. 355(d)), and misbranding provisions, among other requirements, were necessary to avoid further tragedies involving unsafe and ineffective drugs. Using disclaimers for drugs would completely undermine the

regulatory framework established by Congress for the protection of public health. FDA's labeling regulations help ensure the safety and effectiveness of OTC drugs and establish the conditions under which a drug is not misbranded under the FD&C Act. If a manufacturer of a covered sunscreen would like to label its sunscreen product in a way that does not conform to this labeling regulation, it cannot circumvent the premarket NDA process.

In summary, we conclude that the labeling requirements provided in this document do not violate the First Amendment.

F. Other Information

We received submissions requesting that we add a new statement about storage conditions under ''Other information'' in the Drug Facts label (Ref. 1). The submissions argued that sunscreen products in containers are often exposed to heat when used at the beach, swimming pools, etc. The concern expressed in the submissions was that heat could cause sunscreen formulations inside containers to change, resulting in less sun protection. We agree with the submissions. Sunscreen products within containers should not be exposed to direct sun and can be protected by wrapping them in towels and/or keeping them in shaded environments (*e.g.,* under an umbrella and/or in a purse or bag). Consumers could also store sunscreen product containers in coolers while outside during hot periods. In this final rule we are requiring the following statement in the ''Other information'' section of the Drug Facts label: ''[Bullet] protect the product in this container from excessive heat and direct sun'' (new 21 CFR 201.327(f)).

In addition to the statement about storage conditions, we received numerous submissions requesting that we relocate the proposed ''sun alert'' warning to the ''Other information'' section of the Drug Facts label. The submissions argued that the ''sun alert'' is an educational statement and not a warning: ''UV exposure from the sun increases the risk of skin cancer, premature skin aging, and other skin damage. It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen.''

As already discussed, in light of our re-evaluation of the evidence supporting the indications for sunscreens, we have made changes to the labeling to more accurately convey appropriate information to consumers about the benefits, directions, and limitations of two different groups of products covered by the rule—those that provide broad spectrum protection with an SPF value of 15 or higher, and those that do not. We do not agree that this information belongs under the heading ''Other information'' but have included it in modified form under the headings Uses and Directions for products with Broad Spectrum SPF values of 15 or higher (new 201.327(c)(2) and (e)(2), and under a revised ''Skin Cancer/Skin Aging Alert'' under the heading Warnings for other sunscreens (new 201.327(d)(2)).

In this document, we are also removing the optional ''Other information'' statements in proposed 21 CFR 352.52(e):

1. ''Low,'' ''medium,'' ''high'' or ''highest'' ''sunburn protection product''

2. ''Higher SPF products give more sun protection, but are not intended to extend the time spent in the sun.''

According to the 2007 proposed rule, these statements could appear in ''Other information'' or anywhere outside Drug Facts. However, in this rule, we have revised the labeling and are no longer requiring the principal display panel to characterize the level the sunburn protection. Rather, for broad spectrum products, the rule requires only the statement ''Broad Spectrum SPF [fill in tested SPF value]'' to appear on the principal display panel. In light of this revised approach to labeling, we are concerned that including the characterizations of the product as providing ''low,'' ''medium,'' ''high'' or ''highest'' ''sunburn protection would be confusing or misleading, and are no longer including it as an option.

We have concluded that the second statement, although truthful, is not necessary. Consumers likely understand the first part of this statement (higher SPF values represent more sun protection) based on the long-standing inclusion on SPF values on OTC sunscreen products. The second part of the statement (higher SPF products are not intended to extend time spent in the sun) is redundant with the information already provided under ''Uses'' and ''Directions,'' particularly concerning the need for limiting time in the sun (see sections IV.B and IV.D). Although we are not requiring inclusion of the second statement under ''Other information,'' the statement may appear outside the Drug Facts label because it is truthful and nonmisleading.

G. Reduced Labeling

Five submissions requested changes to our proposed regulations allowing reduced labeling for sunscreen products sold in small packages (*i.e.,* packages which meet the requirements in 21 CFR 201.66(d)(10)) that are labeled for use only on small areas of the face. One submission stated that all cosmetic products labeled with sunscreen indications should be required to include all sunscreen product labeling.

After reassessing the criteria for reduced labeling, we are not allowing the reduced labeling included in the 2007 proposed rule. OTC drug labeling regulations (21 CFR 201.66(d)(10)) allow reduced labeling for any OTC drug product sold in a small package, including sunscreen products. In the 2007 proposed rule, we proposed additional reductions in labeling for three types of sunscreen products sold in small packages and intended for use on small areas of the face:

- Proposed 21 CFR 352.52(f)(1)(i)–(f)(1)(iv): Sunscreen products sold in small packages and labeled for use specifically on the lips, nose, ears, and/or around the eyes (*i.e.,* small areas of the face)
- Proposed 21 CFR 352.52(f)(1)(v): Sunscreen-lip protectant combination products sold in small packages
- Proposed 21 CFR 352.52(f)(1)(vi): Sunscreen products formulated as lipsticks, lip products that prolong wear of lipstick, lip gloss, and lip balms

Three submissions argued that we should not restrict labeling exemptions only to sunscreen products sold in small packages and labeled for use on small areas of the face. The submissions stated that reduced labeling provisions should apply to all sunscreen products sold in small packages whether or not they are labeled for use on small parts of the face. Two of the submissions argued that such a restriction violates the Administrative Procedures Act (APA). The submissions cite *Bracco Diagnostics, Inc.,* v. *Shalala* 963 F. Supp. 20, 27–28 (D.D.C. 1997) as evidence that the courts oppose regulations requiring ''two sets of similar products to run down two sets of separate [regulatory] tracks * * * for no apparent reason.''

In this document, we continue to allow the reduced labeling specified in 21 CFR 201.66(d)(10). Therefore, if the information listed under Drug Facts requires more than 60 percent of the total available surface area, the Drug Facts labeling can be reduced by making the formatting changes specified in 21 CFR 201.66(d)(10)(i)–(d)(10)(v). However, in contrast to the 2007 proposed rule, we are not allowing additional reductions in labeling for any sunscreen products.

When we proposed the additional reduced labeling, we recognized that many of the sunscreen products sold in

small packages and labeled for use on small areas of the face could not accommodate full Drug Facts labeling. However, in the last several years, manufacturers have introduced new label designs that permit full Drug Facts labeling on very small packages. For example, some stick products, including lip protectant-external analgesic combinations marketed in 0.15 oz. amounts, have been labeled with wrap-around labels that contain full Drug Facts labeling. If these products can be labeled to accommodate full Drug Facts labeling, then all sunscreen products should be able to accommodate full Drug Facts labeling. Requiring full Drug Facts labeling should not discourage manufacturers from including sunscreen ingredients because of limited labeling space, as stated in the 2007 proposed rule (72 FR 49070 at 49075 through 49077). Therefore, in this document, we are eliminating all of the allowances for reduced labeling in proposed 21 CFR 352.52(f). Sunscreen products can only have reduced labeling for formatting if they meet the criteria in 21 CFR 201.66(d)(10).

V. Miscellaneous Labeling Outside Drug Facts

We received several submissions regarding various performance claims, including comments asking us to allow claims for protection immediately upon application (instant protection) and for extended duration between applications (extended wear) and comments asking us not to allow terms such as ''sunblock,'' ''waterproof,'' and ''sweatproof'' (Ref. 1). These kinds of claims were not included in the 2007 proposed rule (Ref. 1).

We are not including labeling in 21 CFR 201.327 permitting these claims on OTC sunscreen products covered by the rule. The current record does not contain support for any of these kinds of claims. To clarify the status of these kinds of claims, we are finalizing two provisions. We include instant protection and extended wear claims, which are claims that we think may be capable of substantiation, in 21 CFR 310.545(a)(29)(ii). While these claims may not be included on products marketed without approved applications, including them in this provision makes it clear that these claims may be substantiated for an individual product by the submission of adequate data in an NDA.

We agree with the submissions that argue that ''sunblock,'' ''waterproof,'' and ''sweatproof'' claims are false or misleading, as we have stated in previous sunscreen rulemakings (58 FR 28194 at 28228; 64 FR 27666 at 27676 through 27680). These terms are essentially exaggerations of performance that FDA does not think can be substantiated. Accordingly, in this final rule, we codify these as terms or phrases that would be false or misleading on covered products, and are therefore prohibited (21 CFR 201.327(g)).

In addition to submissions requesting that we allow certain labeling outside Drug Facts, we also received a submission requesting that we require information about the UV index (UVI). A stated in the 2007 proposed rule, we have determined that the usage information provided on OTC sunscreen products applies regardless of the UVI value (72 FR 49070 at 49073). Therefore, we will allow but do not require information about the UV index to be included on sunscreen products outside the Drug Facts label.

A submission requested that we require that the UV index appear on sunscreen product labels because this information would help consumers understand and use the UV index to determine their risk of sunburn. The UV index was developed in 1995 by the National Weather Service, Environmental Protection Agency, and Centers for Disease Control and Prevention to provide a forecast of the expected risk of overexposure to UV rays. The UV index is calculated using ozone data, atmospheric pressure, temperature, and cloudiness. As stated in the 2007 proposed rule, we are not requiring labeling of UV index information because it is not necessary for consumers to understand this index in order to safely and effectively use OTC sunscreen products (72 FR 49070 at 49073). However, manufacturers may include truthful and nonmisleading information about the UV index in the labeling outside of Drug Facts if they choose.

We also received a submission requesting that we allow a claim of ''instant protection'' and to allow claims for extended periods of protection between applications (*i.e.,* longer than the 2 hours specified in ''Directions'' in the 2007 proposed rule). The submission argued that several marketed products provide sunburn protection immediately upon application, as demonstrated by test results included in the submissions. In this document, SPF testing requires a 15-minute waiting period between sunscreen application and UV exposure of the test site. It appears that the submitted test method included the same 15-minute waiting period. Therefore, the assertion that this product provides ''instant protection'' does not appear to be substantiated. We also did not receive any data regarding claims for extended periods of use, so it is not clear whether these claims are truthful. Claims that a product provides for an extended period of protection between applications or immediately upon application would have to be supported by data. Therefore, these claims could be made only under approved new drug applications (NDAs) with the required data.

In this document, we are specifically identifying these claims as not allowed on any OTC sunscreen product, regardless of SPF value or broad spectrum protection, without an approved application containing sufficient substantiation to support the claim. (new 21 CFR 310.545(a)(29)(ii)):

- Instant protection or protection immediately upon application
- Claims for ''all-day'' protection or extended wear claims citing a specific number of hours of protection that are inconsistent with the directions for application in 21 CFR 201.327.

In addition, we are identifying the terms ''sunblock'' ''waterproof,'' and ''sweatproof'' as false and misleading, as we have stated in previous sunscreen rulemakings:

- Sunblock (64 FR 27666 at 27679 and 27680)
- Sweatproof (58 FR 28194 at 28227 through 28228)
- Waterproof (58 FR 28194 at 28227 through 28228).

We have previously identified these claims as ones that would render a product misbranded but are addressing them again in this document because OTC sunscreen products currently marketed without approved applications continue to contain the claims. In this final rule, we are listing these false and misleading terms in 21 CFR 201.327(g). These terms may not be included on any OTC sunscreen products covered by the rule.

Finally, in the 2007 proposed rule, we proposed to specify other optional statements that could be included outside of Drug Facts in proposed 21 CFR 352.52(e)(3):

- ''Broad spectrum sunscreen''
- ''Provides [select one of the following: 'UVA and UVB' or 'broad spectrum'] protection''
- ''Protects from UVA and UVB [select one of the following: 'rays' or 'radiation']''
- ''[Select one of the following: 'absorbs' or 'protects'] within the UVA spectrum.''

This final rule is not a monograph, and we do not consider it necessary in this rule to codify optional statements for use outside of ''Drug Facts.'' The labeling required in this document

should provide consumers with the information that they need to safely and effectively use the sunscreen products that it addresses. Under this final rule, products marketed without approved applications that provide broad spectrum protection according to the test in new 21 CFR 201.327(j) of this document will be identified on the PDP by use of the term ''Broad

Spectrum SPF.'' In light of this requirement in the rule for use of the term ''broad spectrum'' on these particular products, including a statement anywhere in the labeling of a product that does not pass the broad spectrum test in 21 CFR 201.327(j) that suggests or implies that the product provides broad spectrum protection would misbrand that product. We likewise caution against references to ''UVA'' (or ''UVA/UVB'') protection on products that do not provide broad spectrum protection as demonstrated by the test in 21 CFR 201.327(j). Such labeling would misbrand the products if it misleadingly suggests that the products provide protection that is equivalent or greater to that provided by products labeled with ''Broad Spectrum SPF'' values or is otherwise false or misleading.

VI. SPF Test Parameters

The 2007 proposed rule included the SPF test from the 1999 final rule with revisions to a few test parameters. In response to the 2007 proposed rule, we received numerous submissions requesting that we revise additional test parameters (Ref. 1). In this document, we have rewritten the regulations describing the SPF test in an effort to make it easier to read and understand and to more closely follow the order in which steps of the SPF testing procedure are conducted. We have also made several revisions to the test parameters. However, we did not make all of the revisions requested in the submissions. Table 4 of this document summarizes test parameters that we considered revising. The table identifies the parameters that we are changing in this document as well as those that we are not changing. Detailed discussion of each test parameter appears throughout the remainder of this section.

TABLE 4—SUMMARY OF SPF TEST PARAMETERS INCLUDED IN THE 2007 PROPOSED RULE AND THIS FINAL RULE

2007 Proposed rule	This final rule
21 CFR 352.70(a). Standard sunscreens	*21 CFR 201.327(i)(2). SPF standard*
Two standards: 8% homosalate (SPF 2—≤15) 7% padimate, 3% oxybenzone (SPF >15)	One standard: 7% padimate, 3% oxybenzone (all SPFs)
HPLC reference standard: no limits set for accuracy of oxybenzone & padimate O	HPLC reference standard: limit set to within 5% of theoretical for accuracy of oxybenzone & padimate O
21 CFR 352.70(b). Light source (solar simulator)	*21 CFR 201.327(i)(1). UV source (solar simulator)*
Emission spectrum specifications: (1) COLIPA [1] 1994 (Ref. 63) (2) no specifications for UVA	Emission spectrum specifications: (1) COLIPA [1] 2006 (Ref. 64) (2) specifications for UVA I and UVA II percentages of total UV
Calibration: every 6 months	Calibration: at least annually
Total irradiance: 1500 Watts/square meter (W/m^2)	Total irradiance: 1500 Watts/square meter (W/m^2)
Beam uniformity: within 20 percent	Beam uniformity: within 20 percent
21 CFR 352.70(c)(7). Number of subjects	*21 CFR 201.327(i)(3). Test subjects*
SPF < 30: 20–25 subjects; ≥ 20 valid results SPF ≥ 30: 25–30 subjects; ≥ 25 valid results	All SPFs: • 10–13 subjects; ≥10 valid results
21 CFR 352.70(c)(4). Test site delineation/subsite	*21 CFR 201.327(i)(4)(i) and (ii). Test site/subsite*
test site area: ≥ 50 cm^2 test subsite area: ≥ 1 cm^2 Distance between subsites: ≥ 1 cm	test site area: ≥ 30 cm^2 test subsite area: ≥ 0.5 cm^2 Distance between subsites: ≥0.8 cm
21 CFR 352.70(c)(5). Application of test materials	*21 CFR 201.327(i)(4)(iii). Applying test materials*
Application amount: 2 milligrams per square centimeter (mg/cm^2) Presaturation of finger cot: Required Water-resistant statement requirements: 20 minute water immersion times 20 minute drying times	Application amount: 2 milligrams per square centimeter (mg/cm^2) Presaturation of finger cot: not required Water-resistant statement requirements: 20 minute water immersion times 15 minute drying times
21 CFR 352.70(d)(3). Determination of individual SPF values	*21 CFR 201.327(i)(5). UV exposure*
Definitions of MED: (1) MED(PS) = MED for protected skin (2) MED(US) = MED for unprotected skin	Definitions of MED: (1) ssMEDp = MED for skin protected by sunscreen standard (2) tpMEDp = MED for skin protected by test product (3) initial MEDu = MED for unprotected skin prior to testing test product (4) final MEDu = MED for unprotected skin determined when testing test product
UV doses for MED(US):	UV doses for initial MEDu:

TABLE 4—SUMMARY OF SPF TEST PARAMETERS INCLUDED IN THE 2007 PROPOSED RULE AND THIS FINAL RULE—Continued

2007 Proposed rule	This final rule
five doses	number of doses not specified
21 CFR 352.70(c)(8) Response criteria	*21 CFR 201.327(i)(5). UV exposure*
Maximal UV exposure:	Maximal UV exposure:
"no more than twice the total energy of the minimal exposure"	not specified

[1] Draft test method entitled "International Sun Protection Factor (SPF) Test Method" developed by the European Cosmetic, Toiletry and Perfumery Association (COLIPA).

We are not making some of the requested changes to certain test parameters because we lack adequate data to determine whether these changes would change the accuracy or reproducibility of the SPF test. We are making changes to some test parameters based on the following developments since the 2007 proposed rule published:

- New data (submitted by the public or published in the scientific literature)
- Technical improvement of SPF testing equipment
- Accumulating experience in the performance of SPF testing
- Efforts towards international harmonization of SPF testing procedures

In support of the requested changes, several submissions (Ref. 1) cited differences between the SPF test in the 2007 proposed rule and the COLIPA SPF test (Ref. 64). The COLIPA SPF test is a joint effort by the cosmetic industry trade associations in Europe, Japan, South Africa, and the United States to harmonize SPF test procedures. The International Organization for Standardization (ISO) is currently developing an SPF test method. Because harmonization of testing methods is important, we are actively involved in the ISO working group responsible for developing methods for assessing the efficacy of sun protection products.

We are revising our proposed SPF test method to be as consistent as possible with the COLIPA SPF test. We acknowledge the merits of harmonizing test methods and are an active participant in ongoing harmonization efforts. However, some of the test parameters in this document differ from comparable parameters in the COLIPA SPF test because we have concluded that the data do not support using the COLIPA SPF test parameters. Throughout the remainder of this section, we discuss whether test parameters in this document match or do not match those in the COLIPA SPF methods.

A. Solar Simulator

Several submissions recommended adopting the solar simulator specifications in the COLIPA SPF test (Ref. 1). We are revising solar simulator specifications to:

- Allow the use of smaller beam, multiport simulators
- Adjust the relative cumulative erythemal effectiveness (RCEE) range specifications for each wavelength band
- Specify that UVA II (320–340 nm) and UVA I (340–400 nm) irradiance should equal or exceed 20 percent and 60 percent, respectively, of the total UV (290–400 nm) irradiance
- Change the regular calibration period from every 6 months to at least once a year

These changes are consistent with the COLIPA SPF test. More importantly, these revisions will allow the SPF test to continue to be accurate and reproducible. For example, we received calibration data demonstrating that solar simulators and their UV lamps are stable for periods longer than 1 year. Therefore, the requirement in the 2007 proposed rule to calibrate every 6 months is unnecessary. The test results should be the same whether calibration is done annually or every 6 months.

In contrast, we are not changing the following solar simulator specifications because changes to these specifications could reduce test accuracy and/or reproducibility:

- Total irradiance limit of 1500 W/m^2
- Total irradiance range of 250–1400 nm
- 20 percent beam uniformity requirement.

These test specifications differ from the COLIPA SPF test, which recommends a 1600 W/m^2 limit and a 10 percent beam uniformity requirement.

Two submissions (Ref. 1) objected to limiting total solar simulator irradiance to 1500 W/m^2 for all wavelengths between 250 and 1400 nm (proposed 21 CFR 352.70(b)(1)). We proposed the 1500 W/m^2 limit because we were concerned that solar simulators operating above this limit could cause excessive heat. Excessive heat could harm test subjects and/or cause loss of dose reciprocity, the correlation between UV dose and resulting erythema. One submission argued that no data indicate that exceeding 1500 W/m^2 causes excessive heat or affects SPF test results. The submission argued that higher intensities should be allowed as long as they are thermally tolerated by test subjects, because allowing higher intensities enables faster SPF testing.

We are not changing the 1500 W/m^2 total irradiance limit. We do not have data demonstrating that exceeding 1500 W/m^2 leads to loss of dose reciprocity. However, we conclude that the limit should be retained to protect test subjects. The COLIPA SPF test cites a study showing that total irradiance of 1600 W/m^2 induces heat and pain in a majority of test subsites, and recommends keeping total irradiance below 1600 W/m^2 (Ref. 64). Therefore, we are keeping the 1500 W/m^2 total irradiance limit (new 21 CFR 201.327(i)(1)(i)).

One submission also objected to the 250–1400 nm range over which total irradiation should be monitored (Ref. 1). The submission argued that portable spectroradiometers are typically incapable of measuring wavelengths out to 1400 nm. According to the submission, emissions from longer wavelengths have not been shown to affect SPF testing.

We are not changing the requirement that total irradiation be monitored over a range of 250–1400 nm. We have concluded that monitoring over this range of wavelengths helps protect SPF test subjects from being exposed to undesirable, unnecessary radiation. The requirement should not impose undue hardship, because longer wavelengths can be monitored using a thermopile, pyroelectric, or similar detectors.

We received two submissions addressing the requirement in proposed 21 CFR 352.70(b)(2) that a solar simulator have "good beam uniformity (within 20 percent) in the exposure plane" (Ref. 1). One submission argued that advances in equipment and monitoring allow for a stricter beam uniformity requirement (<20 percent), which would result in less variability in SPF test results. Another submission argued that the beam uniformity

requirement is only important for large diameter beams and has no impact on SPF testing using small beams.

We are not changing the 20 percent beam uniformity requirement because accurate determination of SPF values relies upon good beam uniformity for all beam sizes. In the 2007 proposed rule, we described how small diameter beams can be tested for beam uniformity (see 72 FR 49070 at 49098). The submission requesting stricter requirements did not include data showing that current solar simulators can reasonably be expected to have beam uniformity less than 20 percent. We conclude that a 20 percent beam uniformity requirement is adequate to produce reliable SPF results. Therefore, we are keeping the requirement that solar simulators demonstrate good beam uniformity (within 20 percent) in new 21 CFR 201.327(i)(1) (iii).

B. Sunscreen Standards

The 2007 proposed rule include two sunscreen standards for use in SPF testing. The two proposed sunscreen standards were a 7 percent padimate O/3 percent oxybenzone standard (mean SPF value of 16.3) and an 8 percent homosalate standard (mean SPF value of 4.47). For SPF testing of sunscreen products with SPF values of 2 to 15, either the padimate O/oxybenzone standard or the homosalate standard would have been required to be tested along with the test sunscreen product. Tests for sunscreen products with SPF values over 15 would have required use of the padimate O/oxybenzone standard.

We received two requests to include an additional sunscreen standard with an SPF value of 30 or higher to test sunscreen products with SPF values of 30 or more (Ref. 1). Neither request specified any particular sunscreen standard formulation with an SPF in this range. If a particular sunscreen standard formulation were specified, we would also need validation data to support including the additional sunscreen standard in the monograph. Therefore, we are not including a sunscreen standard with an SPF value of 30 or more in this document.

We also received a request to include the JCIA SPF 15 'P3' sunscreen standard containing 0.5-percent avobenzone, 3-percent octyl methoxycinnamate, and 2.78-percent phenylbenzimidazole sulfonic acid. To support including the ''P3'' standard, the request included a table showing mean, maximum, and minimum SPF values from tests conducted in labs in Europe, Japan, Australia, and South Africa. We recognize that the ''P3'' standard has been widely used and is included in the COLIPA SPF test, but we are not including the ''P3'' standard in this document. In the 2007 proposed rule (72 FR 49070 at 49095 to 49095), we requested further data to show that testing using the ''P3'' standard could be performed with:

- Low level interlaboratory variation
- Sufficient sensitivity to detect experimental error
- A reasonable degree of accuracy

The submitted data (*i.e.* the table of SPF values) fail to show that the ''P3'' standard meets these performance requirements because they do not show:

- Individual lab results
- The number of tests conducted in each lab
- The number of test subjects used in each test
- Calculated standard errors for each test

Without these data, we cannot assess interlaboratory variability, sensitivity to experimental error, or test result accuracy. In addition, the advantage of using the ''P3'' standard instead of the padimate O/oxybenzone standard is unclear, because both these standards have approximately the same SPF value of 16. Therefore, we are not including the ''P3'' standard in this document.

We are also eliminating the proposed homosalate standard with an SPF value of 4.47 because the padimate O/oxybenzone standard with an SPF value of 16.3 is adequate for validating all test methodologies. In the 2007 proposed rule, we stated that the sunscreen standards were ''method controls rather than calibration tools.'' As a method control, the purpose of the sunscreen standard is verifying proper and consistent performance of test equipment and procedures, rather than verifying the accuracy of the SPF value determined for sunscreen test products. Therefore, we conclude that it is not critical for the SPF value of the sunscreen standard to be close to the SPF value of the sunscreen test product. It is more important that the sunscreen standard demonstrate consistency of test performance. Consequently, we have concluded that including multiple sunscreen standards is unnecessary, and that the padimate O/oxybenzone standard is a suitable sunscreen standard for all sunscreen products. We favor including the padimate O/oxybenzone standard over the homosalate standard because the homosalate standard was only proposed for use for SPF testing of sunscreen products with SPF values lower than 15. Because most currently marketed sunscreen products have SPF values of 15 or higher, the padimate O/oxybenzone standard is used much more frequently than the homosalate standard.

We received one submission identifying errors in the ''Composition of the Padimate O/Oxybenzone Standard Sunscreen'' table that appears in the 2007 proposed rule. As suggested by the submission, we are moving the inactive ingredient ''propylparaben'' from ''Part A'' to ''Part B,'' as it appears in the COLIPA SPF test. We are not revising the listing of the inactive ingredient ''glyceryl monostearate'' to read ''glyceryl monostearate (Glyceryl Stearate SE),'' as suggested. The United States Pharmacopeia defines ''glyceryl monostearate'' as an ''emulsifying and/or solubilizing agent,'' which adequately describes the ingredient that is appropriate for use in the formulation.

C. Test Subjects

In the 2007 proposed rule, we proposed requiring the following numbers of test subjects providing valid results:

- 20 to 25 subjects for sunscreen products with SPF less than 30
- 25 to 30 subjects for sunscreen products with SPF value of 30 or more

We explained that a minimum of 20 subjects would be required to provide an acceptably accurate SPF result (*i.e.,* low standard error of the mean). We had concluded that sunscreen products with SPF values of 30 or more required a greater number of test subjects because we suspected higher test result variability for these sunscreen products. However, the data used for determining appropriate test subject numbers were limited and dated. Therefore, we invited submission of additional data demonstrating what subject numbers would be adequate.

Several submissions recommend requiring 10 to 25 test subjects as in the COLIPA SPF test (Ref. 1). These submissions include data demonstrating that SPF testing can be performed with suitable accuracy and precision with as few as 10 test subjects. The submissions further argued that SPF testing using a minimum of 10 test subjects has been practiced globally for many years, even for sunscreen products with high SPF values.

We agree with the submissions and are lowering the number of test subjects required for SPF testing. We are requiring that a test panel produce a minimum of 10 valid test results. A maximum of three subjects may be rejected from the panel. Therefore, if 3 subjects would be rejected, a test panel would have had to include 13 subjects.

We are reducing the number of test subjects in this document because the

data we received demonstrate that SPF testing can be conducted with adequate accuracy and precision using as few as 10 test subjects, even when testing high SPF products. The submissions include SPF test results for several sunscreen formulations using panels of 20 to 25 test subjects. We randomly selected 10 subjects within each of these panels to determine if using fewer subjects significantly decreased test accuracy and precision. For each of these panels, the mean SPF value and standard error calculated from a randomly selected subset of 10 subjects were not significantly different from those calculated from all 20 to 25 subjects in the panel. Therefore, these data indicate that using as few as 10 test subjects will not compromise SPF test accuracy or precision. Consequently, fewer test sites and subsites need to be tested and fewer test results need to be rejected, thereby decreasing the number of test subjects needed. Our revised SPF test subject number requirement is similar to the COLIPA SPF test requirement. The only significant difference related to test subject number is that we are not including a statistical requirement or allowing individual subjects to be added incrementally to a test panel as allowed under the COLIPA SPF test.

D. Test Sites and Subsites

Several submissions requested the following revisions of the minimum size specifications for test sites and subsites proposed in the 2007 proposed rule (Ref. 1):

- Test site: proposed 50 cm^2 revised to 30 cm^2
- Test subsite: proposed 1 cm^2 revised to 0.5 cm^2
- Subsite separation: proposed 1 cm revised to 0.8 cm

According to the submissions, these smaller revised minimum sizes would allow multiport solar simulators to be used, while the larger proposed sizes would not. These revised specifications have also been adopted in the COLIPA SPF test (Ref. 64).

We are revising the test site and subsite size specifications as requested by these submissions. Our previously proposed specifications were based on single port solar simulators. Some new multiport solar simulators cannot meet these proposed specifications. In the 2007 proposed rule, we stated that reducing test site/subsite size specifications would be considered if data were submitted showing that these reductions would not compromise testing accuracy (72 FR 49070 at 49100). New data show that SPF testing can still be accurately performed using the recommended reduced test site/subsite size specifications (Ref. 1). Therefore, we are revising the test site/subsite size specifications to accommodate new equipment and to harmonize our specifications with global SPF test methods.

E. Finger Cot

In the 2007 proposed rule, we proposed that a finger cot, presaturated with sunscreen, be used to apply the sunscreen in the SPF test (proposed 21 CFR 352.70(c)(5)):

> Use a finger cot compatible with the sunscreen to spread the product as evenly as possible. Pretreat the finger cot by saturating with the sunscreen and then wiping off material before application. Preteatment is meant to ensure that sunscreen is applied at the correct density of 2 mg/cm^2.

We received one submission that objected to the use of finger cots because consumers do not typically use finger cots when applying sunscreens (Ref. 1). Other submissions argued that the presaturation requirement for finger cots is unnecessary and introduces variability in applied amounts (Ref. 1). Other submissions requested the optional use of sponge applicators for testing powder formulations, because they argued that sponge applicators distribute powder formulations more evenly than finger cots (Ref. 1). We are not addressing issues regarding the use of sponge applicators for the testing of powders in this rule. Elsewhere in this issue of the **Federal Register**, we publish an advance notice of proposed rulemaking that discusses sunscreen dosage forms, including powders. We may address this issue in a future rulemaking..

While we acknowledge that consumers do not use finger cots to apply sunscreens, we are continuing to require the use of finger cots in the SPF test. The use of finger cots seems to increase reproducibility of test results, which was why we originally proposed requiring use of finger cots (72 FR 49070 at 49100 through 49101). We agree with the submissions that the presaturation requirement is unnecessary and are removing this requirement. We proposed requiring finger cot presaturation to prevent sunscreen product from adhering to the finger cot instead of being transferred to the test subject's skin, resulting in sunscreen product being applied at less than the intended 2 mg/cm^2. We received study results showing that a residual amount of sunscreen product may adhere to non-presaturated finger cots, but the amount was small (approximately 2 percent) (Ref. 1). In this study, each of 100 finger cots (without presaturation) was weighed before and after sunscreen product application at 2 mg/cm^2 (100 mg sunscreen product applied over 50 cm^2). However, the study did not include a comparison to presaturated finger cots. Therefore, it is difficult to determine the effect of presaturation on residual sunscreen amounts.

In addition, we reassessed the basis for presaturation. We are now concerned that performing the presaturation step may lead to overestimation of SPF values, because the residual amount normally left on a finger cot with presaturation may increase the amount of sunscreen applied to the skin This could lead to overestimation of SPF values. Overestimation of SPF may, in turn, lead to increased incidence of sunburn because consumers may anticipate greater protection than a sunscreen product actually provides. This overestimation risk is a sufficient basis to remove the presaturation step from the proposed SPF test method.

We also received data showing that testing without the presaturation step can produce highly reproducible results (Ref. 1). In a test of 20 subjects without the presaturation step, a control sunscreen product yielded a mean SPF value of 4.19 with a standard error of 0.06 (*i.e.*, 1.4 percent error), while a test sunscreen product yielded a mean SPF value of 15.54 with a standard error of 0.22 (*i.e.*, 1.4 percent error). These errors are small, suggesting that the calculated SPF values did not vary significantly between test subjects. If lack of presaturation increased variability, then the errors would be expected to be larger. Therefore, we are removing the presaturation requirement because of the risk of overestimation of SPF values and our conclusion that the removal of the presaturation step will not affect the reproducibility of SPF test results.

F. Application Amount

We are continuing to require that 2 mg/cm^2 sunscreen product be applied for the SPF test (proposed 21 CFR 352.70(c)(5); new 21 CFR 201.327(i)(4)(iii)). Several submissions argued for a lower application amount that better reflects the actual amount used by consumers, which they argued is commonly 1 mg/cm^2 or less (Ref. 1). These submissions argued that the unrealistically high 2 mg/cm^2 application amount results in SPF values that overstate the actual sun protection provided by the amounts consumers typically apply. Other submissions supported the 2 mg/cm^2 application amount (Ref. 1). These submissions argued that SPF values are relative, not absolute, values that allow comparison of sun protection provided

by different sunscreen products. According to the submissions, changing the application amount will affect the ability of consumers to make this comparison.

We are not changing the sunscreen product application amount because we have concluded that the advantages of continuing to require 2 mg/cm² exceed the disadvantages of lowering the amount. Requiring the 2 mg/cm² sunscreen product application amount is consistent with SPF test methods used in other countries. The 2 mg/cm² application amount is being used in Europe, Australia, Canada, Korea, and Japan (Refs. 65–67). If we lower the application amount, sunscreen products available in the United States will have significantly lower SPF values than similar products available in other countries. This discrepancy in SPF values is counterproductive to our global harmonization efforts and would likely mislead consumers traveling to other countries about the SPF protection of foreign sunscreen products.

Another advantage of continuing to require a 2 mg/cm² sunscreen product application amount is greater reproducibility of SPF test results. Bimczok *et al.* compared the SPF values determined using sunscreen product application amounts of 0.5, 1, and 2 mg/cm² (Ref. 68). The SPF values determined using 2 mg/cm² sunscreen product were more reliable and reproducible than SPF values determined using the lower application amounts. A sunscreen product application amount of 2 mg/cm² is a large enough amount to allow visualization of the distribution of sunscreen product as it is applied. This allows for more consistent and uniform application of the sunscreen used in testing. Therefore, the 2 mg/cm² sunscreen product application amount is more likely to generate reproducible results.

G. Water Resistance

In the 2007 proposed rule, sunscreen products tested with two 20-minute immersion periods (*i.e.*, 40 minutes total) would be allowed to include a ''water resistant'' statement and sunscreen products tested with four 20-minute immersion periods (*i.e.*, 80 minutes total) would be allowed to include a ''very water resistant'' statement. There is a 20-minute drying period between each immersion period. For example, a ''water resistant'' sunscreen product would be tested by having test subjects in the water for 20 minutes, out of the water for 20 minutes, and in the water for 20 minutes.

We received various requests to revise the test (Ref. 1). One submission recommended longer water immersion times equal to those in water resistance tests used in Australia and New Zealand. Another submission included data from an in vitro water resistance test to support removing the in vivo water resistance test. A third submission stated the test should be eliminated because it is not validated and requires too much time. Further, the submission argued that directions for frequent reapplication make the test unnecessary.

We are continuing to include a water resistance test because water resistance is an important property of sunscreen products that can benefit consumers. The water resistance test indicates that a sunscreen product's labeled SPF protection is retained for a certain period of time after immersion in water. This is useful information to consumers. Therefore, we conclude that a water resistance statement based on the test should be allowed (see section III.C of this document).

We are not changing the 20-minute water immersion periods or the number of immersion periods required. We based these time periods on marketing data indicating that individuals at the beach or the pool spend an average of 21 minutes in the water and go into the water an average of 3.6 times (43 FR 38206 at 38263, August 25, 1978). We have not received any other data supporting different time periods. We have concluded that more or longer water immersion periods are not needed.

We are, however, reducing the drying period from 20 minutes to 15 minutes. We are making this change to decrease the time required for testing. Shorter testing time may increase test accuracy and reproducibility, especially for high SPF sunscreens that retain their water resistance for 80 minutes. In addition, 15 minutes is adequate time to allow for drying. It is possible that sunscreens may lose water resistance with repeated wetting and drying. However, we have concluded that a 15-minute drying period mimics consumer behavior and ensures that the water resistant properties of a sunscreen do not change with multiple cycles of water immersion and drying.

VII. SPF Test Issues (Other than Test Parameters)

A. Pass/Fail (Binomial) SPF Test

Several submissions requested the optional use of a pass/fail (binomial) test to determine the SPF value of a sunscreen product (Ref. 1). These submissions promote the pass/fail test because it would expose fewer subjects to UV irradiation, cost less, and save time. The pass/fail test is based on the hypothesis that a sunscreen product of a certain SPF has a 50:50 probability of preventing the MED response when irradiated with a UV dose correlated with that SPF. For example, a sunscreen product with an expected SPF value of 30 or more should prevent the MED response in greater than 50 percent of test subsites irradiated with a UV dose equivalent to 30 times the UV dose that causes the MED response on unprotected skin. If a test sunscreen product prevents the MED response in a significant number of the subsites (*i.e.*, significantly more subsites that ''pass'' versus ''fail''), then the test sunscreen product would be allowed to be labeled with the SPF correlated to the UV dose.

We are not including the optional use of a pass/fail test for SPF testing. We considered a pass/fail SPF test in the 2007 proposed rule (72 FR 49070 at 49094 to 49095). We stated that a pass/fail test could be a reasonable substitute for our proposed SPF test for sunscreen products with SPF values of 30 or more if certain modifications were made and validation data demonstrated that the test could be performed similarly between labs.

In response to our invitation for public comment, one submission included two studies comparing a pass/fail SPF test to the proposed SPF test: (1) A single center study of four sunscreen products with different SPF values and (2) a multicenter (four laboratories) study of two high SPF sunscreen products. After reviewing these data, we have determined that the pass/fail test has the following drawbacks:

- Each test subsite evaluation is biased towards ''pass'' because the evaluator expects that no skin reaction should occur on subsites protected by the test sunscreen product.
- The test fails to reject test sites where all of the subsites show positive responses or all of the subsites show negative responses.
- The validity of treating each subsite as an independent variable is questionable.
- The test endpoint (any observed reaction) differs from the endpoint in the proposed SPF test (clearly defined erythema).
- A passing test result for the sunscreen standard does not demonstrate that the test is being performed correctly.
- Test results do not include data for water resistant sunscreen products.
- Allowing this test as an option would yield products with different UV

protection levels labeled with the same SPF.

- SPF test methods developed by various standards-setting organizations do not include a pass/fail test.
- The study report includes statistical errors that overstate the statistical power of the test to distinguish whether a test sunscreen product provides significant UV protection.

Therefore, we are not including a pass/fail test in the SPF test procedure, because including a pass/fail test would present numerous complications and the available data indicate that a pass/fail test has disadvantages compared to the SPF test included in this document.

B. Photostability

Several submissions expressed concern about the loss of UV protection by sunscreen products due to breakdown of ingredients from exposure to sunlight (Ref. 1). These submissions recommended a test to ensure that sunscreen products exposed to sunlight retain sufficient UV protection. Submitted data show that the composition of sunscreen products can change from exposure to UV radiation. The submissions argue that the published photostability studies are inconclusive because the studies employ artificial test conditions that may not be appropriately extrapolated to actual use of sunscreens:

- Tested sunscreen active ingredients were contained in solutions rather than in typical sunscreen product formulations
- Tested sunscreen products contained active ingredients that are not representative of the active ingredients included in typical sunscreen products
- Products were tested over a limited range of the UV spectrum

The submissions argue that understanding the photostability of sunscreen active ingredients alone is not useful. Rather, the submissions argue that it is critical to understand the photostability of sunscreen active ingredients as part of an overall sunscreen product.

We agree that the available data have limitations. Although the submissions argue that the inconclusive data support including a test for photostability, we have concluded that the data do not justify requiring a photostability test at this time. We are not able to establish specific photostability test procedures or specifications based on the available data. We have not received data validating the performance of a photostability test, nor have we received data demonstrating that the effectiveness of any particular sunscreen product is significantly diminished because of photodegradation. We maintain that the proposed SPF test procedure does account for photostability to some extent, because the SPF test exposes sunscreen products to UV radiation before an SPF value is determined. Consequently, sunscreen products susceptible to photodegradation have correspondingly lower SPF values. One submission argued that the SPF test does not fully account for photostability because the solar simulator emission spectrum is different than natural sunlight. However, this difference is an unavoidable limitation in testing because solar simulators cannot perfectly replicate natural sunlight.

We acknowledge that UV radiation can change the composition of sunscreen products if the products are not photostable, as demonstrated by the submitted data. However, we are not certain that these data are applicable under actual use conditions. The data regarding the effects of UV radiation on the protection provided by sunscreen active ingredients are limited and inconclusive. Therefore, we are not creating a photostability test as part of the SPF test procedure in this document.

C. In Vitro SPF Test

One submission suggested replacing the proposed in vivo SPF test with an in vitro SPF test (Ref. 1). An in vitro SPF test would have advantages of faster performance, lower expense, and no exposure of subjects to UV radiation.

We agree that an in vitro SPF test has these advantages. However, we are not replacing the in vivo SPF test with an in vitro SPF test for the same reasons we stated in the 2007 proposed rule (72 FR 49070 at 49095). One shortcoming of an in vitro test is the lack of data on the performance characteristics of in vitro test substrates, such as quartz or artificial skin. In the 2007 proposed rule, we stated that data failed to show that a substrate adequately mimicked the physiological characteristics of human skin. We stated that we would consider an in vitro test if validating data demonstrated that the performance of the in vitro test was equivalent to the in vivo test. We have not received adequate data to validate an in vitro SPF test. Therefore, we are not including an in vitro test in this document.

D. Anti-Inflammatory Ingredients

One submission recommended requiring a test to verify that sunscreen products do not contain anti-inflammatory ingredients that significantly decrease erythemic response to UV radiation (Ref. 1). The submission did not identify specific anti-inflammatory ingredients. The submission argued that, by decreasing the erythemal response, these ingredients could falsely inflate SPF values determined in SPF testing. In addition, these anti-inflammatory ingredients may increase the likelihood of unwanted harmful effects from sun exposure because sunburn, a cue to avoid sun exposure, would be less evident.

Although the submission raises a serious concern, we are not aware of any data confirming that this problem exists. Therefore, a test to show that anti-inflammatory ingredients may be decreasing erythemic response to UV radiation is not required at this time. It seems unlikely that anti-inflammatory ingredients will affect SPF values because their anti-erythemic effect is relatively short-lived compared to the 16–24 hour interval between UV exposure and erythema observation in the SPF test.

VIII. Broad Spectrum Test

In this document, we are referring to testing involving the UVA part of the spectrum as ''broad spectrum testing.'' The term ''broad spectrum'' more accurately describes the test as covering the full extent of the terrestrial solar UV spectrum (*i.e.,* UVA and UVB radiation). Section VIII.A. of this document provides our rationale for no longer requiring an in vivo test assessing the persistent pigment darkening associated with UVA radiation. Section VIII.B. of this document explains why the in vitro test should be changed from a modified Diffey-Robson ratio to the critical wavelength test. Section VIII.C. defines the testing parameters to be employed in evaluating the critical wavelength of an OTC sunscreen product.

A. In Vivo Test Method: Not Required

We stated in the 2007 proposed rule that an assessment of UVA protection should include determination of both the magnitude and breadth of absorption in the UVA part of the spectrum (72 FR 49070 at 49102 through 49106). We proposed that an in vivo Persistent Pigment Darkening (PPD) test be used to evaluate the magnitude of absorption and an in vitro test be used to evaluate the breadth of absorption. The PPD test, a modification of the PPD test accepted by JCIA [10] since 1996, is almost identical to the SPF test. It is recognized as a standard for the in vivo assessment of UVA protection by the JCIA and the European Commission

[10] Japanese Cosmetic Industry Association.

(Ref. 7). The most significant differences in the PPD test compared to the SPF test are (1) the light source emits only UVA radiation (320–400 nm) and (2) the endpoint is darkening of the skin (tanning) rather than reddening of the skin (erythema).

We have concluded that the PPD test is not necessary to establish that a sunscreen product provides protection against UVA radiation. The magnitude of absorption over the solar terrestrial UV portion of the spectrum (both UVA and UVB) can be effectively assessed based on the SPF test in combination with a pass/fail broad spectrum in vitro test (see Section VIII.B of this document). If sunscreen products pass the in vitro broad spectrum test, then the amount of UVA radiation protection, as well as UVB radiation protection, must increase as the SPF value increases. For example, a Broad Spectrum SPF 40 sunscreen product must provide more UVB and UVA radiation protection than a Broad Spectrum SPF 20 sunscreen product.

For sunscreen products that pass the in vitro broad spectrum test, we have concluded that the SPF and PPD tests are redundant of each other, but we have reasons to prefer the SPF test. The SPF and PPD tests are both clinical and indicative of the magnitude of absorbance of UV radiation. Furthermore, both tests depend on the skin type of the individual. The SPF test measures skin reddening, which is due primarily to UV radiation in the UVB and UVA II regions (290–340 nm). The PPD test measures skin darkening, which is due primarily to UV radiation in the UVA II part of the spectrum (320–340 nm). Therefore, the UV radiation range covered by the PPD test is also covered by the SPF test. In both tests, the endpoint is indicative of how much UV radiation is absorbed. As the magnitude of UV radiation absorbance increases for a sunscreen product, both the SPF and PPD ratings increase.

We have identified several disadvantages of the PPD test as described in the proposed rule (72 FR 49070 at 49103):

- Human subjects are exposed to high doses of UVA radiation with unknown health consequences.
- Exposure to UVA radiation alone (*i.e.,* in the absence of UVB radiation) is never encountered in nature, and the biological effects of such exposure may differ greatly from those due to exposure to natural sunlight.
- Because it is unclear how tanning relates to the harmful effects of sunlight, it is unclear whether persistent pigment darkening represents a clinically meaningful endpoint.

Other disadvantages are pointed out by Nash *et al.* (Ref. 4):

- The physical properties of sunscreen products may differ when sunscreen products are exposed to UVA radiation alone.
- The PPD test is expensive, time consuming, and labor intensive.
- The ability to identify small differences in pigmentation requires a high degree of expertise and interpretation of pigmentation changes will be dependent on the examiner.
- There may be a high degree of variability in test results between subjects in the same test panel as well as between different test panels for the same sunscreen product.
- The test results may not be reproducible between labs.

Because of these disadvantages of conducting the PPD test, and the fact that information obtained from such tests is already provided by SPF testing for sunscreen products that pass the in vitro broad spectrum test, we are eliminating the requirement to conduct a PPD or any other in vivo UVA test in this final rule.

B. In Vitro Test Method: Critical Wavelength

Many submissions objected to our proposal to use a modification of the Boots adaptation of the Diffey/Robson ratio as an in vitro measure of UVA protection (Ref. 1). The Diffey/Robson ratio evaluates UVA protection relative to UVB protection. The ratio is calculated as the area under the absorbance curve in the UVA region (320–400 nm) divided by the area under the absorbance curve in the UVB region (290–320 nm). As the degree of protection against UVA radiation increases, the ratio increases.

We proposed a modification of this ratio to be calculated as the area under the absorbance curve in the UVA I region (340–400 nm) divided by the area under the absorbance curve over total UVB and UVA range (290–400 nm). We indicated that this modification was necessary because we were concerned that a sunscreen product absorbing strongly in the UVA II region (320–340 nm), but not absorbing strongly in the UVA I region, might produce a disproportionately high ratio value (72 FR 49070 at 49105). We would not consider this sunscreen product to be a good broad spectrum sunscreen product even though it has a high ratio value. We noted the importance of ensuring that protection extends well into the UVA I region (340–400 nm), because neither SPF nor PPD measurements provide much information about the longer wavelengths of UVA radiation. Therefore, we modified the ratio to give more emphasis to the UVA I area under the absorbance curve.

Many submissions argued that we should require a determination of critical wavelength rather than the proposed ratio to determine broad spectrum protection (Ref. 1). We agree with the arguments made in the submissions. Therefore, in this document, we are requiring that broad spectrum protection be assessed by determining the critical wavelength of a sunscreen formulation. The submissions noted the following disadvantages with the proposed ratio:

- The proposed ratio places too much emphasis on the UVA I region, which is not generally considered to contribute significantly to the harmful effects of exposure to UV radiation.
- A large ratio could result if one or more ingredients absorb radiation in the shorter wavelength UVA II region but not at all or only minimally in the longer wavelength UVA I region. For example, oxybenzone absorbs radiation at 340–360 nm, and inclusion of this ingredient at higher concentrations might result in a high ratio even though it does not provide true broad spectrum protection.
- The proposed ratio is not a validated measure of UVA protection and is not used anywhere else in the world.
- To achieve high ratios with existing GRASE active ingredients, the concentrations of ingredients that absorb in the UVB and UVA II parts of the spectrum have to be reduced, lowering protection in these parts of the spectrum (*i.e.,* the SPF has to be lowered to increase the ratio).

We agree that our proposed ratio is not the most appropriate in vitro measure of broad spectrum protection. In agreement with many of the submissions, we have concluded that the ratio places too much emphasis on absorption in the UVA I part of the spectrum. Although there is some evidence that UVA I radiation contributes to immune suppression and an increase in p53-positive cells, the effects of UVA I radiation on these processes are 100 to 1000 times less than the effects attributed to UVB and UVA II radiation (Ref. 4). We also acknowledge that there is no experience using the proposed ratio. Further, we received some data in the submissions that demonstrate the need to reduce SPF values in order to achieve high ratio values. We are concerned that, in an effort to gain UVA protection, consumers may be more susceptible to

sunburn because SPF values could be lower in products with higher ratios.

In agreement with many of the submissions, we have concluded that the critical wavelength method provides a better measure of broad spectrum protection. The critical wavelength (λ_c) is derived from the same data as the modified ratio. The critical wavelength is the wavelength at which the area under the absorbance curve represents 90 percent of the total area under the curve in the UV region. This is expressed mathematically as:

$$\int_{290}^{\lambda c} A(\lambda)d\lambda = 0.9\int_{290}^{400} A(\lambda)d\lambda$$

In this expression, A(λ) is the mean absorbance at each wavelength, and dλ is the wavelength interval between measurements.

Like the proposed ratio, the critical wavelength measures the breadth of the UV absorbance curve. Unlike the proposed ratio, the critical wavelength does not emphasize certain parts of the UV spectrum, but is a measure of absorbance across the entire solar terrestrial UV spectrum (UVB and UVA radiation). Sunscreen products offering primarily UVB protection would have a critical wavelength less than 320 nm, whereas those providing both UVB and UVA protection would have critical wavelengths between 320 and 400 nm.

The critical wavelength method is simple, reproducible, and inexpensive. It has been used by sunscreen manufacturers to evaluate UVA protection for over a decade and is one of the most commonly used UVA tests. This is evidenced by the organizations that recommend its use for determining broad spectrum protection, including the European Commission, the American Academy of Dermatology, the American Society for Dermatologic Surgery, and the Skin Cancer Foundation (Ref. 1).

In this document, we are requiring that sunscreen products have a critical wavelength of at least 370 nm (the mean value must be equal to or greater than 370 nm) to be labeled as providing broad spectrum protection (see section VIII.B.). This differs from the tiered rating (low, medium, high, and highest) that we included in the 2007 proposed rule (proposed 21 CFR 352.50(b)(2)). We have concluded that the threshold critical wavelength for a broad spectrum statement should be 370 nm. This wavelength is sufficiently difficult to achieve and will ensure that sunscreen products meeting this threshold provide a significant amount of broad spectrum protection. On the other hand, it is not so difficult to formulate sunscreen products to achieve this critical wavelength that manufacturers cannot develop broad spectrum sunscreen products. We have concluded that UV radiation in the range of 370—400 nm is not very harmful based on the available action spectra for sunburn and skin cancer. We conclude that most of the harmful effects from the sun are caused by UV radiation in the range of 290—370 nm. Further, we conclude that critical wavelength (breadth of UVB and UVA protection) coupled with the SPF value (magnitude of UVB and UVA protection) provides a complete measure of broad spectrum protection provided by a sunscreen product.

C. Critical Wavelength Test Parameters

Although the proposed ratio and critical wavelength calculations are different, both tests are based on the construction of a transmittance curve over the range of UV wavelengths from 290 to 400 nm. We received several submissions requesting that we change or, in some cases, better define aspects of the methodology used to measure transmittance over these wavelengths (Ref. 1). Although the submissions, in most cases, referred specifically to the proposed ratio test, the points made regarding methodology apply equally to the critical wavelength test.

We are making several revisions to the section we referred to as the ''UVA in vitro testing procedure'' in the 2007 proposed rule (proposed 21 CFR 352.71). To more accurately describe the test as covering both the UVB and UVA regions of the spectrum, we now refer to the test as the ''broad spectrum test.'' The revisions are listed in Table 5 in the order in which they appear in this section of the document.

TABLE 5—SUMMARY OF REVISIONS TO THE PROPOSED IN VITRO BROAD SPECTRUM TEST INCLUDED IN THIS FINAL RULE

Revised test parameter	2007 proposed rule	This final rule
Plate	Quartz plate (21 CFR 352.71(b))	PMMA[1] plate (21 CFR 201.327(j)(1)(i))
Term ''spectroradiometer''	Spectroradiometer (21 CFR 352.71(c) and (d))	Spectrometer (21 CFR 201.327(j)(1)(ii), (iv), and (v))
Light source for transmittance measurements.	Solar simulator (21 CFR 352.71(a))	Produce a continuous spectral distribution of UV radiation from 290 to 400 nanometers (21 CFR 201.327(j)(1)(iii)
Input optics: Bandwidth	5 nanometers (21 CFR 352.71(d))	1 nanometer (21 CFR 201.327(j)(1)(iv))
Dynamic range of the spectrometer.	Not specified	Sufficient to measure transmittance accurately through highly absorbing sunscreen (21 CFR 201.327(j)(1)(v))
Application of sunscreen drug product to plate.	2.0 mg/cm^2 with single-phase spreading (21 CFR 352.71(e))	0.75 mg/cm^2 with 2-phase spreading (21 CFR 201.327(j)(2))
Pre-Irradiation dose	Proportional to SPF value (21 CFR 352.71(f))	Fixed at 800 J/m^2-eff (21 CFR 201.327(j)(3))
Number of transmittance measurements.	12 measurements of mean transmittance on 5 different plates (21 CFR 352.71(g) and (i))	5 measurements of mean transmittance on 3 different plates (21 CFR 201.327(j)(4) and (6))
Calculation of critical wavelength.	Not applicable	21 CFR 201.327(j)(7))

[1] Polymethylmethacrylate

We re-organized the broad spectrum test parameters in this final rule so that they are listed in the order that the test is done. This section of the document begins with a description of the plates to be used and the requirements for UV spectrometry. The next section addresses application of the sunscreen product to the plate, and the following section addresses the pre-irradiation procedure. The last sections included under broad spectrum test parameters address measuring the amount of radiation transmitted through the sunscreen product, converting these measurements to absorbance values, and calculating the critical wavelength of a sunscreen product.

All of the proposed test parameters were re-evaluated in the preparation of this document. Some of the parameters did not require revision. Test parameters not revised include:

- Sample holder
- Input optics (other than slit width)
- Light source for pre-irradiation
- Calculation of mean transmittance values
- Calculation of mean absorbance values

The parameters defined in this section are based on our review of submitted data (Ref. 1) and peer-reviewed literature. Wherever possible and consistent with sound science, we have attempted to harmonize the parameters with existing standards, including those of the European Commission (Ref. 7) and COLIPA (Ref. 69). As stated earlier in this document, we are also actively involved in the ISO working group responsible for developing methodologies for assessing sun protection (both UVB and UVA protection).

1. Plate

Many submissions argued that we should specify that roughened PMMA (polymethylmethacrylate) plates be used as a substrate rather than roughened quartz included in the 2007 proposed rule (Ref. 1). The submissions stated that they prefer PMMA plates because these plates are:

- Less expensive than quartz
- Disposable—no need to clean or re-roughen
- Readily available with roughened surface
- Validated in COLIPA ring tests and in widespread use for more than a decade
- Recommended by the European Commission and COLIPA

We agree with these submissions and are specifying, in this document, that PMMA plates be used as the substrate in this document. We are specifying the use of PMMA plates primarily because the vast majority of validation data we have reviewed was collected using PMMA rather than quartz plates. Further, we agree with the submissions noting that PMMA plates are less expensive than quartz and, therefore, can be disposable. The disposability of the PMMA plates will eliminate the requirements for cleaning and re-roughening the surface characteristic of quartz plates.

Consistent with COLIPA, we are also specifying the degree of roughness and size of the application area on these plates. Plates should be roughened on one side to a three-dimensional surface topography measure (Sa) between 2 and 7 micrometers. These Sa values are supported by validation studies (Ref. 70) and are comparable to those recommended by COLIPA (Ref. 69). The application area must be at least 16 square centimeters with no side shorter than 4 centimeters. We are also replacing the word ''substrate'' with the simpler and more widely used term ''plate.''

These changes are included in 21 CFR 201.327(j)(1)(i) of this document. Specifying standardized roughness and size parameters will result in more accurate and reproducible intra- and inter-laboratory measurements of broad spectrum photoprotection. Because these PMMA plates of specified roughness and size are already being used in many parts of the world and are recommended by COLIPA, we have concluded that they can be employed in broad spectrum testing in this country with minimal expense or training of personnel.

2. ''Spectroradiometer'' vs. ''Spectrometer''

Four submissions asked us to replace the term ''spectroradiometer'' with the more generally used term ''spectrophotometer'' (Ref. 1). We originally chose the term ''spectroradiometer'' because UV radiation is not detectable by the human eye and, therefore, is not gauged by photometry (which measures visible light). However, the term ''spectrophotometer'' is often used interchangeably with the term ''spectroradiometer.'' In this document, we are replacing the term ''spectroradiometer'' with the more inclusive term ''spectrometer.'' Use of the term ''spectrometer'' allows the use of either a spectroradiometer or spectrophotometer and will make the language more consistent with current COLIPA guidelines (Ref. 69).

3. Light Source for Transmittance Measurements

Four submissions (Ref. 1) asserted that it is inappropriate to specify a solar simulator as the light source for measuring transmittance (proposed 21 CFR 352.71(a)). Three of the submissions argued that radiation emitted from a solar simulator is filtered such that there is very low energy output in the UV region below 300 nm (Ref. 1). One submission noted that a light source filtered in this way cannot provide sufficient energy to measure transmittance through highly absorbing sunscreen products. The same submission suggested that there may not be enough transmittance at wavelengths less than 300 nm to exceed the noise level of the system even in the absence of a sunscreen product (when transmittance should be maximal).

We agree with the submissions and, in 21 CFR 201.327(j)(1)(iii) of this document, are specifying that the light source for transmittance measurements provide continuous, full spectrum radiation from 290 to 400 nanometers. The use of such a light source should maximize instrument transmission properties while retaining full sensitivity. We note that this type of light source is recommended by COLIPA (Ref. 69).

4. Wavelength Interval Between Transmittance Measurements

Two submissions argued that we should reduce the wavelength intervals between transmittance measurements from the proposed 5 nm to 1 nm (Ref. 1). The submissions stated that specifying a smaller interval would produce more accurate results and noted that current spectrometers are capable of making measurements at 1 nm intervals. We agree with the submissions. Additionally, we are aware that the COLIPA guideline (Ref. 69) specifies that transmittance measurements are to be taken at 1 nm intervals. Therefore, we are revising the required input slit bandwidth in this document to specify that it be less than or equal to 1 nm (new 21 CFR 201.327(j)(1)(iv)). We are also revising the measurement interval (new 21 CFR 201.327(j)(4)) to state that transmittance values should be measured at 1 nm intervals.

5. Dynamic Range of the Spectrometer

We are adding new 21 CFR 201.327(j)(1)(v) to specify that the dynamic range of the spectrometer be ''sufficient to measure transmittance accurately through a highly absorbing sunscreen product at all UV

wavelengths (between 290 and 400 nm).'' The information in this section had been included in the section entitled ''Calculation of the spectral transmittance at each wavelength interval'' in the proposed rule (proposed 21 CFR 352.71(g)). We considered requiring a minimum dynamic range of 2.2 absorbance units, as specified in the COLIPA guidelines (Ref. 69). However, we have concluded that it is not necessary to include this requirement because nearly all current spectrometers are capable of measuring a dynamic range of 2.2 absorbance units or better.

6. Application of Sunscreen Product to PMMA Plate

Thirteen submissions (Ref. 1) expressed one or more concerns over the method by which we proposed applying sunscreen product to the plate (proposed 21 CFR 352.71(e)). Eleven of the thirteen submissions recommended we reduce the amount applied from 2 milligrams per square centimeter (mg/cm^2) to between 0.75 and 1.2 mg/cm^2. Three submissions suggested we specify that the sunscreen product be applied with a better defined spreading action. Two submissions requested we consider requiring that a saturated fingertip be used to apply the product rather than a gloved finger.

We are reducing the application amount in this document because transmittance of UV radiation through a film of 2 mg/cm^2 thickness is low and, therefore, can result in inaccurate and/or irreproducible measures of UVA protection. UV detectors have a range of UV radiation that they can accurately measure referred to as the dynamic range. If UV radiation is outside the dynamic range (either lower or higher), measurements from the detector become less accurate and often less reproducible. We received validation data demonstrating that application amounts lower than 2 mg/cm^2 are more accurate and reproducible than an application of 2 mg/cm^2 (Ref. 1). The 2007 proposed rule required an application amount of 2 mg/cm^2 because this is the amount specified in the proposed in vivo SPF and PPD tests. We are not including the PPD test in this document and we have concluded that consistency with the SPF test is not warranted given the concerns about inaccurate and/or irreproducible results with an application amount of 2 mg/cm^2 in the in vitro UVA method. A reduced application amount is consistent with the COLIPA guidelines (Ref. 69). Both of these documents specify an application amount of 0.75 mg/cm^2. Data we have reviewed from the Personal Care Product Council demonstrate that application of 0.75 to 1.0 mg/cm^2 results in good transmission within the dynamic range of UV detectors (Ref. 1). Therefore, in this document, we are reducing the application amount to 0.75 mg/cm^2 to ensure the UV radiation transmitted through sunscreens is within the dynamic range of UV detectors (21 CFR 201.327(j)(2)).

We are also specifying the type of spreading action to be employed when applying sunscreen product to a plate. One submission noted that the type of spreading action employed would depend on the type of product being applied. The submission argued that it might take 30 seconds to evenly spread thicker water resistant creams, but only 10 seconds to evenly spread lotions or oils. We recognize that the very light spreading action for 10 seconds we proposed may not be sufficient to evenly distribute all dosage forms on a plate (proposed 21 CFR 352.71(e)). One submission provided data from a ring test involving 7 different laboratories showing that the UVAI/UV absorbance ratio is affected by the amount of pressure applied during application. A second submission referenced a paper by Ferrero *et al.* which shows that light pressure applied to some sunscreen products results in different ratios than application with greater pressure (Ref. 70). Both submissions recommended adopting a two-phase application process like that recommended by COLIPA (Ref. 69).

We agree that a two-phase spreading action is a more effective means of achieving a film of uniform thickness and distribution for a variety of sunscreen dosage forms than is the proposed 10 seconds of light spreading. This type of spreading action is more reflective of actual use than the method we proposed. Therefore, we are harmonizing the standard with the COLIPA guidelines by specifying that a two-phase process be used. Section 201.327(j)(2) in this document specifies that ''spreading should be done with a very light spreading action for approximately 30 seconds followed by spreading with greater pressure for approximately 30 seconds.''

Two submissions argued that we should specify a saturated fingertip be used rather than a gloved finger. We do not agree for the reasons specified in section VI.E of this document.

7. Pre-Irradiation Dose

Several submissions expressed concern that the pre-irradiation dose we proposed to account for differences in photostability is too high, particularly if we reduce the application amount (Ref. 1). We proposed that the pre-irradiation dose be proportional to the SPF value of a sunscreen product (proposed 21 CFR 352.71(f)). This was to account for the possibility that consumers may spend more time in the sun with higher SPF products. Proportional pre-irradiation dosing is also recommended in the testing procedure published by COLIPA (Ref. 69). In these documents, the pre-irradiation dose is determined relative to the UVA protection factor. Pre-irradiation dose increases as the UVA protection factor increases.

Two submissions suggested that we use a fixed or absolute dose rather than a relative dose proportional to the SPF value of a sunscreen product (Ref. 1). The submissions noted that, at the same time and location on the earth's surface, all sunscreen products are exposed to the same intensity of sunlight. Therefore, sunscreen products with higher SPF values or UVA protection factors should not be exposed to higher pre-irradiation doses.

We agree with these two submissions. It is appropriate to evaluate sunscreen product photostability using a fixed exposure intensity. We have data demonstrating that avobenzone-containing sunscreen products undergo almost complete photodegradation when exposed to doses between 2 and 3 MEDs [11] (Ref. 71). At a dose of 4 MEDs, there were no further decreases in UVB and UVA absorption of five different sunscreen products containing 2.5- to 3- percent avobenzone. These data reflect the worst case scenario for photodegradation because avobenzone appears to be the least photostable active ingredient in the sunscreen monograph. Therefore, all sunscreen products marketed under the monograph are likely to be completely degraded after 4 MEDs. Based on this data, we are specifying a fixed pre-irradiation dose equivalent to 4 MEDs. As we noted in the 2007 proposed rule, one MED for a skin type II individual is 200 J/m^2-eff (72 FR 49070 at 49107). Therefore, in this document, we are specifying a pre-irradiation dose of 4 times 200 J/m^2-eff (800 J/m^2-eff).

8. Number of Transmittance Measurements

Two submissions (Ref. 1) stated that requiring 12 transmittance measurements on each plate as proposed is excessive and not statistically warranted (proposed 21 CFR 352.71(g)). One submission provided data showing that there are no significant differences in UVAI/UV ratios calculated based on 3, 5, 8, or 12

[11] Minimal erythema dose—the lowest UV dose that produces skin reddening (erythema).

sub-sites per plate. The submission argued that we should reduce the number of required test sites per sample to 6. The other submission proposed that we require only one transmittance measurement per plate. The submission suggested that, rather than taking multiple measurements from several small areas on the plate, one measurement could be made over a relatively broad area.

One of the submissions also argued that it is not necessary to evaluate transmittance on five different plates (proposed 21 CFR 352.71(j)). The submission provided data showing that the UVAI/UV ratio for an SPF 15 sunscreen product is not significantly different whether it is measured on 1, 2, 3, or 5 plates (with 12 measurements per plate). We note that the COLIPA guidelines (Ref. 69) recommend that 3 separate plates be used.

We agree with the submissions that requiring 12 discrete measurements on each plate is not necessary to obtain an accurate transmittance spectrum. The submitted data demonstrate that there are no significant differences in UVAI/UV ratios based on 3, 5, 8, or 12 test sites. Similarly, we agree with the submissions that requiring measurements for five plates is not necessary to obtain an accurate transmittance spectrum. Determining 12 transmittance measurements on five plates, as proposed, results in a total of 60 transmittance measurements. Based on the submitted data, a total of 15 transmittance measurements should produce an accurate transmittance spectrum. Therefore, we are requiring 5 or more measurements on at least 3 different plates (21 CFR 201.327(j)(6) in this document.

9. Determination of Critical Wavelength

Critical wavelength is to be determined as described in section VIII.B of this document.

IX. Analysis of Impacts

A. Final Regulatory Impact Analysis

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). OMB has determined that this final rule is a significant regulatory action under Executive Order 12866. Consistent with Executive Order 13563, the approach taken here maintains ''flexibility and freedom of choice for the public,'' above all by providing ''information for the public in a form that is clear and intelligible.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we lack information characterizing the number of products by firm-size and because most affected entities are considered small, we conclude that this final rule will have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $136 million, using the most current (2010) Implicit Price Deflator for the Gross Domestic Product. We do not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

1. Background

The purpose of this rule is to finalize labeling and testing conditions under which OTC sunscreen drug products marketed without approved applications are not misbranded. This rule addresses labeling and testing requirements for both UVB and UVA radiation protection. The rule modifies the existing SPF test, specifies a test for broad spectrum protection, and requires changes to the product label that affect both the front of the package (the principal display panel or PDP) and the Drug Facts section. In addition, the rule lifts the stay of effective date applied to the 1999 Drug Facts labeling final rule (64 FR 13254) specifically for sunscreen products (66 FR 67485). All manufacturers of sunscreens will incur some labeling costs due to revisions to both the PDP and the Drug Facts section of the product label (see section IX.A.4 of this document). In addition, many manufacturers will incur additional broad spectrum testing costs unless they have already tested their products according to the broad spectrum test required in this rule. Manufacturers of sunscreens will also incur SPF testing costs (see section IX.A.5 of this document). Some manufactures will also have to relabel products that are currently labeled with claims that are not allowed under this final rule (§ 201.327(g) and § 310.545(a)(29)(ii)).

2. Benefits

As discussed in section IV.B of this document, the regular use of a Broad Spectrum SPF 15 or higher sunscreen product, when combined with limiting time in the sun and wearing clothing to protect sun-exposed areas, reduces the risk of skin cancer and early skin aging. The National Cancer Institute estimates that there are more than one million new cases of non-melanoma skin cancer and more than 68,000 new cases of melanoma per year in the United States (Refs. 72 and 73). According to the National Cancer Institute, about 8,700 persons will die of melanoma in 2010. Fatal cases of non-melanoma skin cancer are less common but nonetheless number several hundred per year. The labeling requirements in this rule, in conjunction with implementing the format and content requirements in 21 CFR 201.66, which were stayed for sunscreens but are being lifted in this rule, will provide consumers with clear and concise information about sunscreen use and protection, and about the role of sun exposure in increasing the risk of skin cancer and early skin aging. Consumers will be able to more easily identify products that reduce the risks of skin cancer and early skin aging, when used as directed. The new requirements for product testing will ensure the accuracy of the SPF value and broad spectrum claim on the product label.

Although we are unable to quantify the effects of clear and concise information, the final rule will provide clearer and more consistent information on the benefits of certain sunscreens in regard to skin cancer risk reduction than is available on current labels. By requiring better information on levels of protection, the rule should contribute to reduced exposure to UVB and UVA radiation and thereby reduce the incidence of skin cancer.

The benefits from reduced incidence of skin cancer will equal the value of the illnesses averted. The most appropriate measure of that value is based on the average willingness to pay to reduce the probability of skin cancer. We would then multiply the value per illness averted by the likely number of illnesses averted to determine the benefits of this final rule. Because we lack estimates of the likely numbers of illnesses averted, we present estimates of the value per

illness averted to illustrate the gains per averted case.

We estimated the value per case of preventing skin cancer for fatal and non-fatal cases of melanoma and non-melanoma skin cancer. The estimated average medical cost of treatment, lost productivity, and willingness to pay to avoid some symptoms and other effects represents a plausible lower bound on willingness to pay to avoid a non-fatal case of skin cancer. For melanoma, the estimated total cost is about $2,860 per non-fatal case; for non-melanoma skin cancer, the total cost is about $1,400 per non-fatal case; (Refs. 74 and 75).

The largest potential public health gains from this final rule would likely come from averted deaths. We can calculate the monetary value of averted fatal cases as either the value of statistical lives saved or the value of statistical life-years saved. Although skin cancers occur at all ages, most cases occur at older ages. For that reason, we estimate the benefit from preventing fatal cases using the value of life years saved. According to the National Cancer Institute, the average age of death from melanoma is 68 (Ref. 73); life expectancy for a person between the ages of 68 and 69 is about 16 years (Ref. 76). If we discount the average years of life saved for averted fatal melanoma with rates of 3 and 7 percent, we get discounted statistical life-years saved equal to 12.6 and 9.4 years. The various studies of fatal cases of non-melanoma skin cancer find mean or median ages of death in the 77 to 82 range (Refs. 77–79). The life expectancy for someone between the ages of 79 and 80 is about 9 years (Ref. 76). If we discount the average years of life saved for fatal non-melanoma skin cancers with discount rates of 3 and 7 percent, we get discounted years saved equal to 7.9 and 6.5 years.

In other analyses of life-years saved, we have used values for a statistical life-year in the $107,000 to $322,000 range (74 FR 33030, July 9, 2009; updated to current prices). For this illustrative analysis, we use a medium value of $214,000 per statistical life-year. We multiply the value of a statistical life-year by the discounted life-years saved per fatal case of melanoma, which yields $2.69 million using a 3 percent rate of discount and $2.02 million using a 7 percent rate of discount. If we multiply the value of a statistical life-year by discounted life-years saved per fatal case of non-melanoma skin cancer, we get $1.67 million using a 3 percent rate of discount and $1.39 million using a 7 percent rate of discount.

The development of melanoma and non-melanoma skin cancer from chronic exposure to sunlight, as well as any preventative effects of sunscreen (or any other intervention), occur with a long lag. To estimate the monetary value of an averted case of melanoma or non-melanoma skin cancer through combining other protective measures with increased broad spectrum and at least SPF 15 protection, we adjust for the lag between increased protection and a decrease in the incidence of non-melanoma skin cancer. The only available long-term study finds a minimum lag of 5 years before any significant risk reduction would occur (Refs. 20 and 21). Substantial reductions occur with a much longer lag, probably 15 to 25 years; we use a 20-year lag in this illustrative analysis. With a 20-year lag discounted at 3 percent, the value per averted statistical case of non-fatal melanoma is $1,586; if we discount for at 7 percent, the value per averted case is $740. With a 20-year lag discounted at 3 percent per year, the monetary value per averted statistical case of non-melanoma skin cancer is $773; if we discount at 7 percent, the value per averted case is $361.

For fatal cases, with the 20-year lag discounted at 3 percent per year, the monetary value per averted statistical case of fatal melanoma is $1.49 million; discounted at 7 percent, the value per averted fatal case is $520,000. With a 20-year lag and a 3 percent rate of discount, the discounted value per averted case of non-melanoma skin cancer is $920,000 million; with a 7 percent rate of discount, value per averted fatal case is $360,000.

We have four estimates of the discounted value per averted cases of melanoma and non-melanoma skin cancer, with values corresponded to non-fatal and fatal cases. The annual benefits of this final rule will be the numbers of cases of each type averted multiplied by the value of each type. We do not, however, have estimates of the numbers of actual or statistical cases that will be averted. Although there is wide agreement among experts that the use of more effective sunscreens reduces the risk of sun-related skin cancer, we are unaware of any studies that quantify the reduced risk. Without quantitative estimates of the risk reduction associated with broad spectrum protection, we are unable to quantity the overall effects of this final rule on public health.

3. Number of Products Affected

Estimating the number of products affected by this rule is difficult because we do not have complete data on the number of OTC sunscreen products currently marketed. Our Drug Listing System does not have accurate information on the number of marketed OTC sunscreen products. In the 2007 proposed rule (72 FR 49070 at 49108), we estimated that there were about 3,000 OTC sunscreen drug products, including cosmetic products containing sunscreen, with about 12,000 SKUs.[12]

In response to the 2007 proposed rule, we received a submission arguing that our estimates of the number of products and SKUs were low but the submission did not suggest a corrected value. We contracted with the consulting firm Eastern Research Group (ERG) to profile the sunscreen market and assess the cost to reformulate a sunscreen product. ERG's full report can be found in Docket No. FDA–1978–N–0018 (Ref. 80). ERG did an extensive search using the internet and other sources and found fewer dosage forms and SKUs than we had estimated. ERG estimates that there are about 3,065 to 3,600 SKUs. More recently, the new FDA labeling cost model estimates that about 3,591 sunscreen SKUs are marketed, with up to 2,348 different formulations. Because these data are based on a recent survey of the market, we conclude that they are more representative of the number of products affected than the estimates in the proposed rule. For this analysis, we therefore use 3,591 SKUs to represent the number of affected sunscreen labels and 2,348 for the number of formulations.

To comply with the rule, sunscreen products currently marketed as providing broad spectrum protection that were already tested using the test method in this rule will have to be re-labeled but will not have to be retested for broad spectrum protection. Other products will be tested for broad spectrum protection and, if they pass and, will be relabeled with the broad spectrum protection claim. Manufacturers may also choose to reformulate their products to pass the test or discontinue production of the products.

We have not attributed any reformulation costs to this final rule but realize that some manufacturers may choose to reformulate their product if it does not pass the broad spectrum test.

4. Cost To Relabel Sunscreen Products

The cost to relabel varies greatly depending on the printing method and number of colors used. In the 2007 proposed rule, we stated that the majority of sunscreen products are packaged in plastic bottles or tubes with the label printed directly on the

[12] SKUs refers to ''stock keeping units,'' which are individual products, packages, and sizes.

container or applied as a decal or paper label during the packaging process.

The labeling requirements in this rule will change both the PDP and the Drug Facts section of the package and are considered a major redesign. Frequent label redesigns are typical for OTC sunscreen products, with redesigns generally implemented every 1 to 2 years. If a scheduled redesign coincides with relabeling required by this rule, the incremental labeling cost will be lower than if the labeling change takes place before scheduled changes. To estimate the cost to relabel, we are assuming that all products will be relabeled and none are discontinued.

In the 2007 proposed rule, we used a model developed for us by the consulting firm RTI International to derive an estimate of the cost to relabel sunscreen products (Ref. 81). The model was developed to estimate the cost of food labels, which are similar to the labels on the products affected by this final rule. In response to the 2007 proposed rule, we received a submission disagreeing with our estimates of how sunscreens are packaged and the cost to relabel these products (Ref. 1). The submission argued that many sunscreen products, particularly sunscreen-cosmetic combinations, have a secondary container and, therefore, an additional label. The submission also argued that some sunscreen products would require a fold-out label or new secondary carton to accommodate the labeling required in this rule. Furthermore, the submission argued that relabeling these products would cost $15,000 to $17,000 per SKU. The submission did not include any data or information to support its estimate.

We agree that cosmetic packaging and labeling is generally more costly than OTC drug labeling. We also agree that manufacturers of sunscreen-cosmetic products would use the packaging norm of the cosmetic industry because those are the products they are competing with. The cost estimates we are using now demonstrate a large variation in the price per SKU to account for the differences in packaging. If the standard content and format changes required by the OTC labeling final rule (64 FR 13254) are being implemented for the first time, there could be increases in the size of container and carton labels. Since we are allowing, in this rule, for a compliance period of 1 year for most products but 2 years for products with low sales volume ($25,000 annually), inventory losses for unused packaging and labels are minimized and accounted for in this analysis.

For this final rule, we use the new FDA labeling cost model developed by RTI International, which includes estimates for changing sunscreen labels. The one-time costs for a major labeling change to sunscreen labels are $7,454 to $18,785, depending on the type of labeling and packaging. The medium estimate is $11,572 per major labeling changes. These costs include mostly labor and materials, with some cost for lost inventory.

We estimate that the timing of scheduled relabeling will coincide with the relabeling required by this rule for 50 percent of the 3,591 SKUs . We estimate the total labeling cost for the SKUs with coinciding scheduled redesign would be minimal administrative costs or about $550 ($310 to $790). Therefore, the total one-time cost for relabeling would be about $13.9 million to $35.1 million, with a medium estimate of $21.8 million (1,796 × $11,572 + 1,796 × $550).

5. Cost To Test or Retest Products To Determine SPF Values

Manufacturers will incur SPF testing costs because the rule requires labeling for OTC sunscreen products to include SPF values determined in accordance with the specific test method that it describes. We will publish draft guidance entitled ''Guidance for Industry: Enforcement Policy—OTC Sunscreen Drug Products Marketed Without An Approved Application'' that describes our intended enforcement policy regarding these OTC sunscreen products. In the draft guidance, we propose to exercise enforcement discretion for a period of 2 years after the publication of this final rule with regard to the SPF testing requirements for certain OTC sunscreen products on the market prior to June 17, 2011. We estimate that 65 to 75 percent of sunscreen reformulations, or 1,526 to 1,761 will require SPF retesting. The cost of an SPF test depends on whether the product is also making water resistance claims and the SPF value being tested; the cost of water resistant testing is much higher than static testing (see Table 6). In their analysis of the sunscreen market ERG found that about 5 percent of products claimed water resistance and SPF values less than 30, 3 percent of products claimed water resistance with SPF greater than 30, while the remaining 92 percent could use the static SPF test. We use those percentages to estimate total SPF testing costs of $3.2 to $5.9 million (see Table 6). The midpoint of estimated SPF testing costs is $4.6 million.

TABLE 6—COST OF SPF TESTING

Type of test	Estimated number of formulations		Cost of test		*Total cost*	
	Low	High	Low	High	Low	High
Water resistant, SPF < 30	76	88	$4,500	$4,860	$343,395	$427,923
Water resistant, > 30	46	53	4,500	5,130	260,037	271,018
SPF static test	1,404	1,620	1,900	3,240	2,667,798	5,249,189
Total Cost for SPF testing					3,217,230	5,948,130

6. Cost to Test or Retest Products for Broad Spectrum Protection

In the proposed rule, we estimated that about 75 percent of sunscreen products would need to be tested for broad spectrum protection. We received a submission arguing that our estimate was too low and that at least 90 percent of products would need to be tested (Ref. 1). The argument in the submission was based on the four-tier UVA star rating in the proposed rule. The submission stated that sunscreen products with ''low,'' one-star protection would need to be tested. We have now changed the rating criteria to pass-fail, where a critical wavelength of at least 370 nm is necessary to make the broad spectrum statement. Over the years, there has been a steady increase in the number of products with claims of broad spectrum protection. A recent survey of marketed products found that 65 percent of the products surveyed met the criteria for the broad spectrum statement (Ref. 82). Products that were tested in accordance with the broad

spectrum test in this rule would not need to be re-tested.

Because the broad spectrum test in this rule is different than the proposed test, we assume that all affected products would need to be tested. In the 2007 proposed rule, we estimated a one-time testing cost of approximately $5.4 million for products that have broad spectrum protection claims. This estimate was based on 2,250 sunscreen products (75 percent of marketed products) being tested with a test cost of $2,400. The test costs were estimated as $2,200 for the proposed in vivo test and $200 for the proposed in vitro test. In this rule, we are not requiring the in vivo test.

In response to the proposed rule, we received two submissions arguing that our estimate of $200 for the cost of the in vitro test was too low (Ref. 1). The first submission states that the cost of an in vitro test is $500, and the second states that the cost is $800. The first submission, from a sunscreen manufacturer, states that $500 is the price charged by an independent testing laboratory to test its product. The second submission does not provide any basis for its estimate. Although the in vitro test in this rule is different than the in vitro test in the 2007 proposed rule, the cost to conduct the tests is the same. ERG found that the cost of the test ranges from $300 to $800 (Ref. 80). Assuming all affected marketed product formulations (1,526 to 1,761 formulations) will be tested for broad spectrum protection at a cost ranging from $300 to $800, the total cost to test sunscreen products for broad spectrum protection is estimated to be $457,860 to $1,408,800 [(1,526 × $300) to (1,761 × $800)].

7. Total Incremental Costs

Because we took steps earlier to mitigate the impact of labeling changes on the sunscreen industry by staying the requirements in earlier rules, the labeling costs in this rule incorporate the labeling costs from three final rules:

1. 1999 OTC drug labeling final rule (64 FR 13254)

2. 1999 Sunscreen final rule (64 FR 27666)

3. This rule.

Manufacturers were able to postpone compliance costs when we chose to stay the labeling requirements for the 1999 final rule that standardized the format and content requirements for labeling OTC drug products (21 CFR part 201), which would have become effective for all sunscreens by 2005 (69 FR 53801). We include, as part of labeling costs, the cost of increased container labels and package size to accommodate the Drug Facts format.

The estimated total one-time incremental cost of this rule range $17.6 to 42.5 million [($13.9 million labeling cost + $3.2 million SPF testing cost + $0.5 million broad spectrum testing cost) to ($35.1 million labeling cost + $5.9 million SPF testing cost + $1.4 million broad spectrum testing cost)]. The medium estimated one-time incremental costs are $27.3 million. Annualized over 10 years, the costs are $2.1 to $5 million using a 3 percent rate of discount and $2.5 to $6.1 million using a 7 percent rate of discount. Annualized medium costs are $3.2 million using a 3 percent rate of discount and $3.9 million using a 7 percent rate of discount. If some manufacturers of sunscreen products have already complied with the 1999 final rule and would not otherwise have to relabel products as a result of this final rule, then these estimates may overstate actual total costs.

8. Analysis of Alternatives

The principal alternatives we identified were the inclusion of several provisions from the 2007 proposed rule. In the 2007 proposed rule, we required in vivo and in vitro tests for determining UVA protection. In this rule, we have eliminated the in vivo test requirement, reducing compliance costs by about $5 million. We also proposed labeling on the PDP that would indicate the level of UVA protection. In this rule, we changed the in vitro test to one that measures both UVB and UVA protection (*i.e.,* broad spectrum protection). We also established a pass/fail broad spectrum protection statement on the PDP in place of a UVA rating.

We considered requiring a negative statement on the PDP indicating that a product did not have broad spectrum protection if it failed the in vitro test. Numerous submissions from manufacturers opposed this requirement, and we are concerned that the statement could be misinterpreted by consumers. Moreover, as noted previously, this alternative is beyond the scope of this final rule, which applies only to products that do provide broad spectrum protection.

B. Small Business Impact (Final Regulatory Flexibility Analysis)

We estimate that about 78 percent of the approximately 100 domestic companies that manufacture OTC sunscreen products would be considered small business entities (defined by the Small Business Administration as having fewer than 750 employees). Because most affected entities are considered small, we conclude that this final rule will have a significant economic impact on a substantial number of small entities. Consequently, this analysis, together with other relevant sections of this document, serves as the Final Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

The average one-time incremental cost per firm will be about $185,000 to $445,000, with a medium of about $285,000. This burden, described in more detail in section IX.A of this document, includes labeling costs, SPF testing costs, and broad spectrum testing costs. The economic impact will vary by firm, depending on the number of products requiring testing and the number of SKUs requiring labeling. Also, firm-specific impact will vary inversely with the product sales; the per firm burden will be lower for firms with products with high sales volumes. Because the relative economic impact of product retesting is greater for products with lower sales volume, which could disproportionately affect smaller firms, we are providing a longer implementation period (2 years) for products with annual sales of less than $25,000. Because the OTC drug industry is highly regulated, all firms are expected to have access to the necessary professional skills on staff or to have contractual arrangements to comply with the testing requirements of this rule.

X. Paperwork Reduction Act of 1995

This final rule contains certain information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Specifically, the final rule establishes requirements for SPF labeling based on specified testing of covered products, (21 CFR 201.327(a)(1) and (i)). This rule also lifts the delay of implementation date for § 201.66 (21 CFR 201.66), the general OTC Drug Facts labeling format regulation, which has applied to all OTC sunscreen products (69 FR 53801). The information collections associated with § 201.66 have been approved in accordance with the PRA under OMB Control Number 0910–0340, but this approval does not currently include application of these provisions to OTC sunscreens. (76 FR 9022, February 16, 2011). The lifting of the stay of effective date of § 201.66 for OTC sunscreens will modify this information collection.

Elsewhere in this issue of the **Federal Register**, in accordance with section 3506(c)(2)(A) of the PRA (44 U.S.C.

3506(c)(2)(A)), we are publishing a 60-day notice soliciting public comment on the collections of information resulting from this final rule and will then submit these information collection provisions to OMB for approval. These requirements will not be effective until we obtain OMB approval. We will publish a notice concerning OMB approval of these requirements in the **Federal Register** prior to the effective date of this final rule.

With the exceptions noted above, we conclude that the other provisions of this rule are not subject to OMB review under the PRA. Section 201.327 contains specific labeling information, including directions and warnings, which are a ''public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)) and, therefore, are not collections of information. The requirements for obtaining certain medical history information and informed consent from test subjects (21 CFR 201.327(i)(3)(ii) and (i)(3)(iv)) are not collections of information because information collected from subjects of clinical testing does not constitute information under 5 CFR 1320.3(h)(5). There are no recordkeeping provisions associated with the SPF and broad spectrum testing (*i.e.,* effectiveness testing) described in this rule. The burdens of SPF testing as relevant to labeling (third party disclosures) are addressed in the notice published elsewhere in this issue of the **Federal Register**.

XI. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to ''construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.'' The sole statutory provision giving preemptive effect to the final rule is section 751 of the FD&C Act (21 U.S.C. 379r). We have complied with all of the applicable requirements under the Executive order and have determined that the preemptive effects of this rule are consistent with Executive Order 13132.

XIII. References

The following references are on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857, under Docket No. FDA–1978–N–0018 (formerly 1978N–0038) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified all Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.

1. FDA List of Docket Submissions Addressed in This Rule; Organized by Issue.

2. *The United States Pharmacopeia 31–National Formulary 26,* The United States Pharmacopeial Convention, Inc., MD, p., 3547, 2009.

3. *The United States Pharmacopeia 31–National Formulary 26,* The United States Pharmacopeial Convention, Inc., MD, p., 3548, 2009.

4. Nash, J. F. *et al.,* ''Ultraviolet A Radiation: Testing and Labeling for Sunscreen Products,'' *Dermatologic Clinics,* 24:63–74, 2006.

5. Sayre, R. M. *et al.,* ''Commentary on 'UVB–SPF': the SPF Labels of Sunscreen Products Convey More Than Just UVB Protection,'' *Photodermatology Photoimmunology Photomedicine,* 24:218–220, 2008.

6. Vainio, H. and F. Bianchini, ''Cancer-Preventive Effects of Sunscreens'' in *IARC Handbooks of Cancer Prevention: Volume 5 Sunscreens,* IARC, Lyon, FR, 69–124, 2001.

7. ''Commission Recommendation of 22 September 2006 on the Efficacy of Sunscreen Products and the Claims Made Relating Thereto,'' *Official Journal of the European Union, L265,* 49:39–43, 2006.

8. Document No. FDA–1978–N–0018–0692 in Docket No. FDA–1978–N–0018.

9. Calvacca, L., ''Screening the New Sunscreens,'' *Working Woman,* 15:120–123, 1990.

10. Fourtanier, A. *et al.,* ''Sunscreens Containing the Broad-Spectrum UVA absorber, Mexoryl SX, Prevent the Cutaneous Detrimental Effects of UV Exposure: A Review of Clinical Study Results,'' *Photodermatology, Photoimmunology, and Photomedicine,* 24:164–174, 2008.

11. De Gruijl, F., ''UV Radiation, DNA Damage, Mutations, and Skin Cancer'' in *Environmental UV Radiation: Impact on Ecosystems and Human Health and Predictive Models,* Springer, Netherlands, 249–258, 2006.

12. Lucas, R. *et al., ''Solar Ultraviolet Radiation. Global Burden of Disease from Solar Ultraviolet Radiation'', Environmental Burden of Disease Series No. 13,* World Health Organization, 2006.

13. Armstrong, B. K. *et al.,* ''Sun Exposure and Skin Cancer,'' *Australasian Journal of Dermatology,* 38:S1–S6, 1997.

14. World Health Organization, IARC, ''IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 55. Solar and Ultraviolet Radiation,'' *http://monographs.iarc.fr/ENG/Monographs/vol55/volume55.pdf,* September 1, 2009.

15. ''Report on Carcinogens, Eleventh Edition,'' *http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724–F1F6–975E–7FCE50709CB4C932,* October 13, 2009.

16. Rabe, J. *et al.,* ''Photoaging: Mechanisms and Repair,'' *Journal of the American Academy of Dermatology,* 55:1–19, 2006.

17. Reynolds, K.D., *et al.,* ''Predictors of Sun Exposure in Adolescents in a Southeastern U.S. Population,'' *Journal of Adolescent Health,* 19:409–415, 1996.

18. Robinson, J.K., D.S. Rigel, and R.A. Amonette, ''Summertime Sun Protection Used by Adults for Their Children,'' *Journal of the American Academy of Dermatology,* 42:746–753, 2000.

19. Ulrich, C., *et al.,* ''Prevention of Non-Melanoma Skin Cancer in Organ Transplant Patients by Regular Use of a Sunscreen: A 24 Months, Prospective, Case-Control Study,'' *British Journal of Dermatology,* 161:78–84, 2009.

20. Green, A. *et al.,* ''Daily Sunscreen Application and Betacarotene Supplementation in Prevention of Basal-Cell and Squamous-Cell Carcinomas of the Skin: A Randomized Controlled Trial,'' *The Lancet,* 354:723–729, 1999.

21. van der Pols, J. C. *et al.,* ''Prolonged Prevention of Squamous Cell Carcinoma of the Skin by Regular Sunscreen Use,'' *Cancer Epidemiology, Biomarkers, and Prevention,* 15:2546–2548, 2006.

22. Habif, T. P. *et al.,* ''Premalignant and Malignant Nonmelanoma Skin Tumors'' in *Skin Disease Diagnosis and Treatment,* Mosby, St. Louis, MO, 360–395, 2001.

23. Araki, K. *et al.,* ''Incidence of Skin Cancers and Precancerous Lesions in Japanese. Risk Factors and Prevention,'' *Journal of Epidemiology,* 9:S14–S21, 1999.

24. Darlington, S. *et al.,* ''A Randomized Controlled Trial to Assess

Sunscreen Application and Beta Carotene Supplementation in the Prevention of Solar Keratoses,'' *Archives of Dermatology,* 139:451–455, 2003.

25. Naylor, M. F. *et al.,* ''High Sun Protection Factor Sunscreens in the Suppression of Actinic Neoplasia,'' *Archives of Dermatology,* 131:170–175, 1995.

26. Thompson, S. C. *et al.,* ''Reduction of Solar Keratoses by Regular Sunscreen Use,'' *New England Journal of Medicine,* 329:1147–1151, 1993.

27. Gallagher, R. P. *et al.,* ''Broad-Spectrum Sunscreen Use and the Development of New Nevi in White Children: A Randomized Controlled Trial,'' *The Journal of the American Medical Association,* 283:2955–2960, 2000.

28. Lee, T. K. *et al.,* ''Site-Specific Protective Effect of Broad-Spectrum Sunscreen on Nevus Development Among White Schoolchildren in a Randomized Trial,'' *Journal of the American Academy of Dermatology,* 52:786–792, 2005.

29. Seite, S. and A. Fourtanier, ''The Benefit of Daily Photoprotection,'' *Journal of the American Academy of Dermatology,* 58:S160–S166, 2008.

30. Fourtanier, A. *et al.,* ''Protection of Skin Biological Targets by Different Types of Sunscreens,'' *Photodematology, Photoimmunology, and Photomedicine,* 22:22–32, 2006.

31. Young, A. R. *et al.,* ''The Detrimental Effects of Daily Sub-Erythemal Exposure on Human Skin In Vivo Can Be Prevented by a Daily-Care Broad-Spectrum Sunscreen,'' *Journal of Investigative Dermatology,* 127:975–978, 2007.

32. Moyal, D. D. and A. M. Fourtanier, ''Broad-Spectrum Sunscreens Provide Better Protection From Solar Ultraviolet-Simulated Radiation and Natural Sunlight-Induced Immunosuppression In Human Beings,'' *Journal of the American Academy Dermatology,* 58:S149–54, 2008.

33. ''Label Information for Alli™ Weight Loss Aid,'' *http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021887lbl.pdf,* November 23, 2009.

34. ''Your Guide to Lowering Your Cholesterol with TLC. Therapeutic Lifestyle Changes,'' *NIH Publication No. 06–5235,* 2005.

35. ''Lipitor'' in *Physicians' Desk Reference,* ed., Thomson Healthcare Inc., Montvale, NJ, 2457–2462, 2008.

36. ''The Risks of Tanning,'' *http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/Tanning/ucm116432.htm,* October 21, 2009.

37. Dowdy, J. C. *et al.,* ''Indoor Tanning Injuries: An Evaluation of FDA Adverse Event Reporting Data,'' *Photodermatology Photoimmunology Photomedicine,* 25:216–220, 2009.

38. Holick, M. F. and T. C. Chen, ''Vitamin D Deficiency: A Worldwide Problem with Health Consequences,'' *The American Journal of Clinical Nutrition,* 87:1080S–1086S, 2008.

39. Cable News Network, ''Vitamin D is Hot! Here's How to Get it,'' *http://www.cnn.com/2008/HEALTH/diet.fitness/05/20/cl.vitamin.d/index.html,* October 31, 2008.

40. Holick, M. F., ''Sunlight, UV–Radiation, Vitamin D and Skin Cancer: How Much Sunlight do We Need?,'' *Advances in Experimental Medicine and Biology,* 624:1–15, 2008.

41. Maxwell, J. D., ''Seasonal Variation in Vitamin D,'' *Proceedings of the Nutrition Society,* 53:533–543, 1994.

42. Salih, F. M., ''Effect of Clothing Varieties on Solar Photosynthesis of Previtamin D3: An in Vitro Study,'' *Photodermatology, Photoimmunology, and Photomedicine,* 20:53–58, 2004.

43. Webb, A. R., ''Who, What, Where and When-Influences on Cutaneous Vitamin D Synthesis,'' *Progress in Biophysics and Molecular Biology,* 92:17–25, 2006.

44. Institute of Medicine, ''Vitamin D'' in *Dietary Reference Intakes For Calcium, Phosphorus, Magnesium, Vitamin D, And Flouride,* National Academies Press, Washington, DC, 250–287, 1997.

45. Wolpowitz, D. and B. A. Gilchrest, ''The Vitamin D Questions: How Much Do You Need And How Should You Get It?,'' *Journal of the American Academy of Dermatology,* 54:301–17, 2006.

46. Matsuoka, L. Y. *et al.,* ''Sunscreens Suppress Cutaneous Vitamin D3 Synthesis,'' *Journal of Clinical Endocrinology and Metabolism,* 64:1165–1168, 1987.

47. Matsuoka, L. Y. *et al.,* ''Chronic Sunscreen Use Decreases Circlulating Concentrations of 25-hydroxyvitamin D. A preliminary Study,'' *Archives of Dermatology,* 124:1802–1804, 1988.

48. Marks, R. *et al.,* ''The Effect of Regular Sunscreen Use on Vitamin D Levels in an Australian Population. Results of a Randomized Controlled Trial,'' *Archives of Dermatology,* 131:415–421, 1995.

49. Farrerons, J. *et al.,* ''Clinically Prescribed Sunscreen (Sun Protection Factor 15) Does not Decrease Serum Vitamin D Concentration Sufficiently Either to Induce Changes in Parathyroid Function or in Metabolic Markers,'' *British Journal of Dermatology,* 139:422–427, 1998.

50. Kimlin, M. *et al.,* ''Does a High UV Environment Ensure Adequate Vitamin D Status?'' *Journal of Photochemistry and Photobiology B. Biology,* 89:139–147, 2007.

51. Cusack, C *et al.,* ''Photoprotective Behavior and Sunscreen Use: Impact on Vitamin D Levels in Cutaneous Lupus Erythematosus,'' *Photodermatology, Photoimmunology, and Photomedicine,* 24:260–267, 2008.

52. Hoesl, M. *et al.,* ''Vitamin D Levels of XP–Patients Under Stringent Sun Protection,'' *European Journal of Dermatology,* 20:457–460, 2010.

53. Zerwekh, J. E., ''Blood Biomarkers of Vitamin D Status,'' *American Journal of Clinical Nutrition,* 87:1087S–1091S, 2008.

54. The American Academy of Dermatology, ''Sun Protection for Children,'' *http://www.aad.org/public/publications/pamphlets/sun_sunprotection.html,* February 1, 2009.

55. The American Academy of Dermatology, ''Actinic Keratoses,'' *http://www.aad.org/public/publications/pamphlets/sun_actinic.html,* February 1, 2009.

56. The American Academy of Dermatology, ''The Sun and Your Skin,'' *http://www.aad.org/public/publications/pamphlets/sun_sun.html,* February 1, 2009.

57. The American Academy of Dermatology, ''The Darker Side of Tanning,'' *http://www.aad.org/public/publications/pamphlets/sun_darker.html,* February 1, 2009.

58. The American Academy of Dermatology, ''Skin Cancer,'' *http://www.aad.org/public/publications/pamphlets/sun_skin.html,* February 1, 2009.

59. Centers for Disease Control and Prevention, ''Sunscreen for Your Sun Day,'' *http://www.cdc.gov/cancer/skin/chooseyourcover/index.htm,* October 23, 2009.

60. ''Sunwise Program: Action Steps for Sun Safety,'' *http://www.epa.gov/sunwise/actionsteps.html,* February 1, 2009.

61. Wright, M.W. *et al.,* ''Mechanisms of Sunscreen Failure,'' *Journal of the American Academy of Dermatology,* 44:781–784, 2001

62. Rigel, D., ''American Academy of Dermatology's Melanoma/Skin Cancer Detection and Prevention Month Press Release,'' April 25, 2001.

63. European Cosmetic, Toiletry and Perfumery Association (COLIPA); JCIA; CTFA–SA; CTFA, ''Sun Protection Factor Test Method,'' 1994.

64. European Cosmetic, Toiletry and Perfumery Association (COLIPA); JCIA; CTFA–SA; CTFA, ''International Sun

Protection Factor (SPF) Test Method,'' 2006.

65. Standards Australia and Standards New Zealand, ''Australian/New Zealand Standard Sunscreen Products Evaluation and Classification,'' AS/NZS 2604:1998,'' 1998.

66. Health Canada, ''Category IV Monograph Sunburn Protectants. Procedure for Determining an SPF,'' 2002.

67. Korea Food and Drug Administration, ''Korean Measurement Standards for UV Protection Efficacy,'' 2001.

68. Bimczok, R. *et al.,* ''Influence of Applied Quantity of Sunscreen Products on the Sun Protection Factor—A Multicenter Study Organized by the DGK Task Force Sun Protection,'' *Skin Pharmacology and Physiology,* 20:57–64, 2007.

69. COLIPA (The European Cosmetics Association), ''Method for the In Vitro Determination of UVA Protection Provided by Sunscreen Products,'' *COLIPA Guidelines,* 2007a.

70. Ferrero, L. *et al.,* ''Importance of Substrate Roughness for In Vitro Sun Protection Assessment,'' *IFSCC Magazine,* 9:97–108, 2006.

71. Sayre, R. M. and J. C. Dowdy, ''Photostability Testing of Avobenzone,'' *Cosmetics and Toiletries,* 114:85–91, 1999.

72. National Cancer Institute, ''Skin Cancer,'' *http://www.cancer.gov/cancertopics/types/skin,* April 17, 2009.

73. National Cancer Institute, ''Surveillance Epidemiology and End Results: Melanoma of the Skin,'' *http://seer.cancer.gov/statfacts/html/melan.html,* November 10, 2010.

74. Bickers, D.R. *et al.,* ''The Burden of Skin Diseases: 2004,'' *Journal of the American Academy of Dermatology,* 55:490–500, 2006.

75. Freedberg, K.A. *et al.,* ''Screening for Mealignant Melanoma: A Cost-Effective Analysis,'' *Journal of the American Academy of Dermatology,* 41:738–745, 1999.

76. Arias, E., B.L. Rostron, and B. Tejada-Vera, ''United States Life tables, 2005,'' National Vital Statistics Reports, 58:1–132, 2010.

77. Lewis, K.G. and M.A. Weinstock, ''Nonmelanoma Skin Cancer Mortality (1988–2000),'' *Archives of Dermatology,* 140:837–842, 2004.

78. Nolan, R.C., M. T.-L. Chan, and P.J. Heenan, ''A Clinicopathologic Review of Lethal Nonmelanoma Skin Cancers in Western Australia,'' *Journal of the American Academy of Dermatology,* 52:101–108, 2005.

79. Girschik, J. *et al.,* ''Deaths from Non-Melanoma Skin Cancer in Western Australia,'' *Cancer Causes & Control,* 19:879–885, 2008.

80. Eastern Research Group (2010) ''Sunscreen Drug Formulations for Over-the-Counter Human Use,'' Task Order No. 21, Contract No. 223–03–8500.

81. RTI International, ''FDA Labeling Cost Model, Final Report,'' prepared by Mary Muth, Erica Gledhill, and Shawn Karns, RTI. Prepared for Amber Jessup, FDA Center for Food Safety and Applied Nutrition, Revised January 2003.

82. ''Sunscreen Market Analysis: The Evolution and Use of UVA–1 Actives,'' The Proctor and Gamble Company, Sharon Woods Technical Center, Cincinatti, OH, 2004.

List of Subjects

21 CFR Part 201

Drugs, Incorporation by reference, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

PART 201—LABELING

■ 1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

■ 2. Section 201.327 is added to subpart G to read as follows:

§ 201.327 Over-the-counter sunscreen drug products; required labeling based on effectiveness testing.

The following provisions apply to sunscreen products containing aminobenzoic acid, avobenzone, cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, oxybenzone, padimate O, sulisobenzone, titanium dioxide, trolamine salicylate, or zinc oxide, alone or in combination. The provisions do not apply to sunscreen products marketed under approved new drug applications or abbreviated new drug applications.

(a) *Principal display panel.* In addition to the statement of identity in paragraph (b) of this section, the following labeling shall be prominently placed on the principal display panel:

(1) *Effectiveness claim.* (i) *For products that pass the broad spectrum test in paragraph (j) of this section.* (A) The labeling states ''Broad Spectrum SPF [insert numerical SPF value resulting from testing under paragraph (i) of this section]''.

(B) *Prominence.* The Broad Spectrum SPF statement shall appear as continuous text with no intervening text or graphic. The entire text shall appear in the same font style, size, and color with the same background color.

(ii) *For sunscreen products that do not pass the broad spectrum test in paragraph (j) of this section.* The labeling states ''SPF [insert numerical SPF value resulting from testing under paragraph (i) of this section]''. The entire text shall appear in the same font style, size, and color with the same background color.

(2) *Water resistance statements.* (i) *For products that provide 40 minutes of water resistance according to the test in paragraph (i)(7)(i) of this section.* The labeling states ''Water Resistant (40 minutes)''.

(ii) *For products that provide 80 minutes of water resistance according to the test in paragraph (i)(7)(ii) of this section.* The labeling states ''Water Resistant (80 minutes)''.

(b) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the drug as a ''sunscreen.''

(c) *Indications.* The labeling of the product states, under the heading ''Uses,'' the phrases listed in this paragraph (c), as appropriate. Other truthful and nonmisleading statements, describing only the uses that have been established and listed in this paragraph (c), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) relating to misbranding and the prohibition in section 301(d) of the FD&C Act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the FD&C Act.

(1) For all sunscreen products, the following indication statement must be included under the heading ''Uses'': ''[Bullet] helps prevent sunburn''. See § 201.66(b)(4) of this chapter for definition of bullet.

(2) For sunscreen products with a Broad Spectrum SPF value of 15 or higher according to the tests in paragraphs (i) and (j) of this section, the labeling may include the following statement in addition to the indication in § 201.327(c)(1): ''[Bullet] if used as directed with other sun protection measures (see Directions [in bold italic

font]), decreases the risk of skin cancer and early skin aging caused by the sun''.

(3) Any labeling or promotional materials that suggest or imply that the use, alone, of any sunscreen reduces the risk of or prevents skin cancer or early skin aging will cause the product to be misbranded under section 502 of the FD&C Act (21 U.S.C. 352).

(d) *Warnings.* The labeling of the product contains the following warnings under the heading ''Warnings''.

(1) *For all sunscreen products.* (i) The labeling states ''Do not use [bullet] on damaged or broken skin''.

(ii) The labeling states ''When using this product [bullet] keep out of eyes. Rinse with water to remove.''

(iii) The labeling states ''Stop use and ask a doctor if [bullet] rash occurs''.

(2) *For sunscreen products that are broad spectrum with SPF values of at least 2 but less than 15 according to the SPF test in paragraph (i) of this section or that do not pass the broad spectrum test in paragraph (j) of this section.* The first statement under the heading ''Warnings'' states ''Skin Cancer/Skin Aging Alert [in bold font]; Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, not [in bold font] skin cancer or early skin aging.''

(e) *Directions.* The labeling of the product contains the following statements, as appropriate, under the heading ''Directions.'' More detailed directions applicable to a particular product formulation may also be included.

(1) *For all sunscreen products.* (i) As an option, the labeling may state ''For sunscreen use:''.

(ii) The labeling states ''[bullet] apply [select one of the following: 'Liberally' or 'generously'] [and, as an option: 'And evenly'] 15 minutes before sun exposure''.

(iii) As an option, the labeling may state ''[bullet] apply to all skin exposed to the sun''.

(iv) The labeling states ''[bullet] children under 6 months of age: Ask a doctor''.

(2) *For sunscreen products with a Broad Spectrum SPF value of 15 or higher according to the tests in paragraphs (i) and (j) of this section.* The labeling states ''[bullet] Sun Protection Measures. [in bold font] Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a Broad Spectrum SPF value of 15 or higher and other sun protection measures including: [Bullet] limit time in the sun, especially from 10 a.m.–2 p.m. [bullet] wear long-sleeved shirts, pants, hats, and sunglasses''.

(3) *For products that satisfy the water resistance test in paragraph (i)(7) of this section.* The labeling states ''[bullet] reapply: [Bullet] after [select one of the following determined by water resistance test: '40 minutes of' or '80 minutes of'] swimming or sweating [bullet] immediately after towel drying [bullet] at least every 2 hours''.

(4) *For products that do not satisfy the water resistance test in paragraph (i)(7) of this section.* The labeling states ''[bullet] reapply at least every 2 hours [bullet] use a water resistant sunscreen if swimming or sweating''.

(f) *Other information.* The labeling of the product contains the following statement under the heading ''Other information:'' ''[bullet] protect the product in this container from excessive heat and direct sun''.

(g) *False and misleading claims.* There are claims that would be false and/or misleading on sunscreen products. These claims include but are not limited to the following: ''Sunblock,'' ''sweatproof,'' and ''waterproof.'' These or similar claims will cause the product to be misbranded under section 502 of the FD&C Act (21 U.S.C. 352).

(h) *Labeling of products containing a combination of sunscreen and skin protectant active ingredients.* Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. Labeling provisions in § 347.50(e) of this chapter shall not apply to these products.

(i) *SPF test procedure.* (1) *UV source (solar simulator).* (i) *Emission spectrum.* A single port or multiport solar simulator should be filtered so that it provides a continuous emission spectrum from 290 to 400 nanometers (nm) with a limit of 1,500 Watts per square meter (W/m^2) on total irradiance for all wavelengths between 250 and 1,400 nm.

(A) The solar simulator should have the following percentage of erythema-effective radiation in each specified range of wavelengths:

SOLAR SIMULATOR EMISSION SPECTRUM

Wavelength range (nm)	Percent erythemal contribution [1]
< 290	< 0.1
290–300	1.0–8.0
290–310	49.0–65.0
290–320	85.0–90.0
290–330	91.5–95.5
290–340	94.0–97.0
290–400	99.9–100.0

[1] Calculation of erythema action spectrum described in § 201.327(i)(1)(ii) of this section.

(B) In addition, UVA II (320–340 nm) irradiance should equal or exceed 20 percent of the total UV (290–400 nm) irradiance. UVA I (340–400 nm) irradiance should equal or exceed 60 percent of the total UV irradiance.

(ii) *Erythema action spectrum.* (A) Calculate the erythema action spectrum weighting factor (V_i) at each wavelength λ:

(*1*) $V_i(\lambda) = 1.0$ ($250 < \lambda \leq 298$ nm)

(*2*) $V_i(\lambda) = 10^{0.094 * (298 - \lambda)}$ ($298 < \lambda \leq 328$ nm)

(*3*) $V_i(\lambda) = 10^{0.015 * (140 - \lambda)}$ ($328 < \lambda$ 400 nm)

(B) Calculate the erythema-effective UV dose (E) delivered by a solar simulator as follows:

$$E = \sum_{250}^{400} V_i(\lambda) * I(\lambda) * t$$

Where $V_i(\lambda)$ = erythema action spectrum weighting factor at each wavelength λ
$I(\lambda)$ = irradiance (Watts per square meter) at each wavelength λ
t = exposure time (seconds)

Erythema-effective dose (E) is expressed as effective Joules per square meter (J/m^2-eff).

(C) The emission spectrum must be determined using a handheld radiometer with a response weighted to match the spectrum in ISO 17166 CIE S 007/E entitled ''Erythemal reference action spectrum and standard erythema dose,'' dated 1999 (First edition, 1999–12–15; corrected and reprinted 2000–11–15), which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. You may obtain a copy from the ISO Copyright Office, Case Postale 56, CH–1211, Geneva 20, Switzerland, telephone +41–22–749–01–11 or fax +41–22–74 -09–47. *http://www.iso.org.* You may inspect a copy at the Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993, call 301–796–2090, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://*

www/archives.gov/federal_register/code_offederal_regulations/ibr_locations.html. The solar simulator output should be measured before and after each phototest or, at a minimum, at the beginning and end of each test day. This radiometer should be calibrated using side-by-side comparison with the spectroradiometer (using the weighting factors determined according to paragraph (i)(1)(ii)(A) of this section) at the time of the annual spectroradiometric measurement of the solar simulator as described in paragraph (i)(1)(iv) of this section.

(iii) *Operation.* A solar simulator should have no significant time-related fluctuations (within 20 percent) in radiation emissions after an appropriate warm-up time and demonstrate good beam uniformity (within 20 percent) in the exposure plane. The delivered dose to the UV exposure site must be within 10 percent of the expected dose.

(iv) *Periodic measurement.* To ensure that the solar simulator delivers the appropriate spectrum of UV radiation, the emission spectrum of the solar simulator should be measured at least annually with an appropriate and accurately calibrated spectroradiometer system (results should be traceable to the National Institute for Standards and Technology). In addition, the solar simulator must be recalibrated if there is any change in the lamp bulb or the optical filtering components (*i.e.,* filters, mirrors, lenses, collimating devices, or focusing devices). Daily solar simulator radiation intensity should be monitored with a broadband radiometer with a response weighted to match the erythema action spectrum in ISO 17166 CIE S 007/E entitled ''Erythemal reference action spectrum and standard erythema dose,'' which is incorporated by reference in paragraph (i)(1)(ii)(C) of this section. If a lamp must be replaced due to failure or aging during a phototest, broadband device readings consistent with those obtained for the original calibrated lamp will suffice until measurements can be performed with the spectroradiometer at the earliest possible opportunity.

(2) *SPF standard.* (i) *Preparation.* The SPF standard should be a formulation containing 7-percent padimate O and 3-percent oxybenzone.

COMPOSITION OF THE PADIMATE O/OXYBENZONE SPF STANDARD

Ingredients	Percent by weight
Part A:	
Lanolin	4.50
Cocoa butter	2.00
Glyceryl monostearate	3.00
Stearic acid	2.00
Padimate O	7.00
Oxybenzone	3.00
Part B:	
Purified water USP	71.60
Sorbitol solution	5.00
Triethanolamine, 99 percent	1.00
Methylparaben	0.30
Propylparaben	0.10
Part C:	
Benzyl alcohol	0.50
Part D:	
Purified water USP	QS [1]

[1] Quantity sufficient to make 100 grams.

Step 1. Add the ingredients of Part A into a suitable stainless steel kettle equipped with a propeller agitator. Mix at 77 to 82 °C until uniform.

Step 2. Add the water of Part B into a suitable stainless steel kettle equipped with a propeller agitator and begin mixing at 77 to 82 °C. Add the remaining ingredients of Part B and mix until uniform.

Step 3. Add the batch of Step 1 to the batch of Step 2 and mix at 77 to 82 °C until smooth and uniform. Slowly cool the batch to 49 to 54 °C.

Step 4. Add the benzyl alcohol of Part C to the batch of Step 3 at 49 to 54 °C. Mix until uniform. Continue to cool batch to 35 to 41 °C.

Step 5. Add sufficient water of Part D to the batch of Step 4 at 35 to 41 °C to obtain 100 grams of SPF standard. Mix until uniform. Cool batch to 27 to 32 °C.

(ii) *HPLC assay.* Use the following high performance liquid chromatography (HPLC) procedure to verify the concentrations of padimate O and oxybenzone in the SPF standard:

(A) *Instrumentation.* (*1*) Equilibrate a suitable liquid chromatograph to the following or equivalent conditions:

(*i*) Column	C–18, 250 millimeters (mm) length, 4.6 mm inner diameter (5 microns)
(*ii*) Mobile Phase.	85:15:0.5 methanol: water: acetic acid
(*iii*) Flow Rate	1.5 milliliters (mL) per minute
(*iv*) Temperature.	Ambient
(*v*) Detector	UV spectrophotometer at 308 nanometers
(*vi*) Attenuation.	As needed

(*2*) Use HPLC grade reagents for mobile phase.

(B) *Preparation of the HPLC reference standard.* (*1*) Weigh 0.50 gram (g) of oxybenzone USP reference standard into a 250-mL volumetric flask. Dissolve and dilute to volume with isopropanol. Mix well.

(*2*) Weigh 0.50 g of padimate O USP reference standard into a 250-mL volumetric flask. Dissolve and dilute to volume with isopropanol. Mix well.

(*3*) Pipet 3.0 mL of the oxybenzone solution and 7.0 mL of the padimate O solution into a 100-mL volumetric flask. Dilute to volume with isopropanol and mix well.

(C) *HPLC system suitability.* (*1*) Make three replicate 10-microliter injections of the HPLC reference standard (described in paragraph (i)(2)(ii)(B) of this section). The relative standard deviation in peak areas should not be more than 2.0 percent for either oxybenzone or padimate O.

(*2*) Calculate the resolution (R) between the oxybenzone and padimate O peaks from one chromatogram as follows:

$$R = \frac{2 * (to - tp)}{Wo + Wp}$$

Where t_o = retention time for oxybenzone
t_p = retention time for padimate O
W_o = oxybenzone peak width at baseline
W_p = padimate O peak width at baseline

If the resolution (R) is less than 3.0, adjust the mobile phase or replace the column.

(D) *SPF standard assay.*

(*1*) The SPF standard is diluted to the same concentration as the HPLC reference standard according to the following steps:

(i) Step 1. Weigh 1.0 g of the SPF standard (described in paragraph (i)(2)(i) of this section) into a 50-mL volumetric flask.

(ii) Step 2. Add approximately 30 mL of isopropanol and heat with swirling until contents are evenly dispersed.

(iii) Step 3. Cool to room temperature (15 to 30 °C) and dilute to volume with isopropanol. Mix well.

(iv) Step 4. Pipet 5.0 mL of the preparation into a 50-mL volumetric flask and dilute to volume with isopropanol. Mix well.

(*2*)(*i*) Inject 10-microliter of diluted SPF standard from paragraph (i)(2)(D)(*1*) of this section and calculate the amount of oxybenzone and padimate O as follows:

$$\text{Percent Oxybenzone} = \frac{\text{Peak area of oxybenzone in sunscreen standard}}{\text{Peak area of oxybenzone in HPLC reference standard}} * 100$$

$$\text{Percent Padimate O} = \frac{\text{Peak area of padimate O in sunscreen standard}}{\text{Peak area of padimate O in HPLC reference standard}} * 100$$

(ii) The percent of oxybenzone and padimate O in the SPF standard should be between 95 and 105.

(3) *Test subjects.* (i) *Number of subjects.* A test panel should include enough subjects to produce a minimum of 10 valid test results. A maximum of three subjects may be rejected from this panel based on paragraph (i)(5)(v)) of this section.

(ii) *Medical history.* (A) Obtain a medical history from each subject with emphasis on the effects of sunlight on the subject's skin. Determine that each subject is in good general health with skin type I, II, or III as follows:

(*1*) Always burns easily; never tans (sensitive).

(*2*) Always burns easily; tans minimally (sensitive).

(*3*) Burns moderately; tans gradually (light brown) (normal).

(*4*) Burns minimally; always tans well (moderate brown) (normal).

(*5*) Rarely burns; tans profusely (dark brown) (insensitive).

(*6*) Never burns; deeply pigmented (insensitive).

(B) Skin type is based on first 30 to 45 minutes of sun exposure after a winter season of no sun exposure. Determine that each subject is not taking topical or systemic medication that is known to alter responses to UV radiation. Determine that each subject has no history of sensitivities to topical products and/or abnormal responses to sunlight, such as a phototoxic or photoallergic response.

(iii) *Physical examination.* Conduct a physical examination to determine the presence of sunburn, suntan, scars, active dermal lesions, and uneven skin tones on the areas of the back to be tested. A suitable source of low power UVA, such as a Woods lamp, is helpful in this process. If any of these conditions are present, the subject is not qualified to participate in the study. The presence of nevi, blemishes, or moles will be acceptable if, in the physician's judgment, they will neither compromise the study nor jeopardize a subject's safety. Subjects with dysplastic nevi should not be enrolled. Excess hair on the back is acceptable if the hair is clipped. Shaving is unacceptable because it may remove a significant portion of the stratum corneum and temporarily alter the skin's response to UV radiation.

(iv) *Informed consent.* Obtain legally effective written informed consent from all test subjects.

(4) *Sunscreen application.* (i) *Test site.* Test sites are locations on each subject's back, between the beltline and the shoulder blades (scapulae) and lateral to the midline, where skin responses to UV radiation are determined. Responses on unprotected skin (no test material applied) and protected skin (sunscreen test product(s) or SPF standard applied) are determined at separate unprotected and protected test sites, respectively. Test sites should be randomly located in a blinded manner. Each test site should be a minimum of 30 square centimeters and outlined with indelible ink.

(ii) *Test subsite.* Test subsites are the locations to which UV radiation is administered within a test site. At least five test subsites should receive UV doses within each test site. Test subsites should be at least 0.5 square centimeters (cm^2) in area and should be separated from each other by at least 0.8 cm. Each test subsite should be outlined with indelible ink.

(iii) *Applying test materials.* Apply the sunscreen test product and the SPF standard at 2 milligrams per square centimeter (mg/cm^2) to their respective test sites. Use a finger cot compatible with the sunscreen to spread the product as evenly as possible.

(iv) *Waiting period.* Wait at least 15 minutes after applying a sunscreen product before exposing the test sites to UV radiation as described in paragraph (i)(5)) of this section. For water resistant sunscreen products, proceed with the water resistance testing procedure described in paragraph (i)(7) of this section after waiting at least 15 minutes.

(5) *UV exposure.* (i) *Definition of minimal erythema dose (MED).* The minimal erythema dose (MED) is the smallest UV dose that produces perceptible redness of the skin (erythema) with clearly defined borders at 16 to 24 hours after UV exposure. The MED for unprotected skin (MED_u) is determined on a test site that does not have sunscreen applied. The MED for protected skin (MED_p) is determined on a test site that has sunscreen applied. An MED_p is determined for the SPF standard ($ssMED_p$). An MED_p is determined for the sunscreen test product ($tpMED_p$).

(ii) *UV exposure for initial* MED_u. For each test subject, administer a series of UV radiation doses expressed as J/m^2-eff (as determined according to paragraph (a)(2) of this section) to the test subsites within an unprotected test site using an accurately calibrated solar simulator. Select doses that are a geometric series represented by 1.25^n (*i.e.,* each dose is 25 percent greater than the previous dose).

(iii) *UV exposure for final* MED_u, $ssMED_p$, and $tpMED_p$. For each subject, determine the final MED_u, $ssMED_p$, and $tpMED_p$ by administering a series of five UV doses to the appropriate test sites. The middle dose (X) in each of these dose series (*i.e.,* the third dose) should equal the initial MED_u times the expected SPF. Note that the expected SPF equals 1 and 16.3 for the final MED_u and $ssMED_p$, respectively. The remaining UV doses in the series depend upon the expected SPF value of the sunscreen test product(s).

For products with an expected SPF less than 8, administer UV doses that increase by 25 percent with each successive dose (*i.e.,* 0.64X, 0.80X, 1.00X, 1.25X, and 1.56X). For products with an expected SPF from 8 to 15, administer UV doses that increase by 20 percent with each successive dose (*i.e.,* 0.69X, 0.83X, 1.00X, 1.20X, and 1.44X). For products with an expected SPF higher than 15, administer UV doses that increase by 15 percent with each successive dose (*i.e.,* 0.76X, 0.87X, 1.00X, 1.15X, and 1.32X).

(iv) *Evaluation of test subsites.* In order that the person who evaluates the test subsites is not biased, he/she should not be the same person who applied the sunscreen drug product to the test site or administered the UV doses. After UV doses are administered, all immediate responses should be recorded. These may include an immediate darkening or tanning, typically grayish or purplish in color, which fades in 30 to 60 minutes; an immediate reddening at the subsite, due to heating of the skin, which fades rapidly; and an immediate generalized heat response, spreading beyond the subsite, which fades in 30 to 60

minutes. After the immediate responses are noted, each subject should shield the exposed area from further UV radiation until the MED is determined. Determine the MED 16 to 24 hours after UV exposure. Because erythema is evaluated 16 to 24 hours after UV exposure, the final MED_u, $ssMED_p$, and $tpMED_p$ are typically determined the day following determination of the initial MED_u. Evaluate the erythema responses of each test subsite using either tungsten or warm white fluorescent lighting that provides at least 450 lux of illumination at the test site. For the evaluation, the test subject should be in the same position as when the test site was irradiated.

(v) *Invalid test data.* Reject test data for a test subject if erythema is not present on either the unprotected or protected test sites; or erythema is present at all subsites; or the responses are inconsistent with the series of UV doses administered; or the subject was noncompliant (*e.g.,* the subject withdraws from the test due to illness or work conflicts or does not shield the exposed testing sites from further UV radiation until the MED is determined).

(6) *Determination of SPF.* (i) Calculate an SPF value for each test subject (SPF_i) as follows:

$$SPFi = \frac{MEDp}{MEDu}$$

(ii) Calculate the mean

$$SPF\ (\overline{SPF})$$

and the standard deviation (s) from the SPF_i values. Calculate the standard error (SE), which equals $s/\sqrt{n}$ (where n equals the number of subjects who provided valid test results). Obtain the t value from Student's t distribution table corresponding to the upper 5-percent point with n—1 degrees of freedom. Determine the labeled SPF value, which equals the largest whole number less than

$$\overline{SPF} - (t * SE).$$

In order for the SPF determination of a test product to be considered valid, the SPF value of the SPF standard should fall within the standard deviation range of the expected SPF (*i.e.,* 16.3 ± 3.43).

(7) *Determination of water resistance.* The following procedure should be performed in an indoor fresh water pool, whirlpool, and/or hot tub maintained at 23 to 32 °C. Fresh water is clean drinking water that meets the standards in 40 CFR part 141. The pool and air temperature and the relative humidity should be recorded.

(i) *Water resistance (40 minutes).* The labeled SPF should be determined after 40 minutes of water immersion using the following procedure:

(A) Step 1: Apply the sunscreen as described in paragraph (d) of this section.

(B) Step 2: Perform moderate activity in water for 20 minutes.

(C) Step 3: Rest out of water for 15 minutes. Do not towel test site(s).

(D) Step 4: Perform moderate activity in water for 20 minutes.

(E) Step 5: Allow test sites to dry completely without toweling.

(F) Step 6: Apply the SPF standard as described in paragraph (d) of this section.

Step 1. Expose test sites to UV doses as described in paragraph (e) of this section.

(ii) *Water resistance (80 minutes).* The labeled SPF should be determined after 80 minutes of water immersion using the following procedure:

(A) Step 1: Apply the sunscreen as described in paragraph (d) of this section.

(B) Step 2: Perform moderate activity in water for 20 minutes.

(C) Step 3: Rest out of water for 15 minutes. Do not towel test site(s).

(D) Step 4: Perform moderate activity in water for 20 minutes.

(E) Step 5: Rest out of water for 15 minutes. Do not towel test site(s).

(F) Step 6: Perform moderate activity in water for 20 minutes.

(G) Step 7: Rest out of water for 15 minutes. Do not towel test site(s).

(H) Step 8: Perform moderate activity in water for 20 minutes.

(I) Step 9: Allow test sites to dry completely without toweling.

(J) Step 10: Apply the SPF standard as described in paragraph (d) of this section.

(K) Step 11: Expose test sites to UV doses as described in paragraph (e) of this section.

(j) *Broad spectrum test procedure.* (1) *UV Spectrometry.* (i) *Plate.* Use optical-grade polymethylmethacrylate (PMMA) plates suitable for UV transmittance measurements. The plate should be roughened on one side to a three dimensional surface topography measure (Sa) between 2 and 7 micrometers and must have a rectangular application area of at least 16 square centimeters (with no side shorter than 4 cm).

(ii) *Sample holder.* The sample holder should hold the PMMA plate in a horizontal position to avoid flowing of the sunscreen drug product from one edge of the PMMA plate to the other. It should be mounted as close as possible to the input optics of the spectrometer to maximize capture of forward scattered radiation. The sample holder should be a thin, flat plate with a suitable aperture through which UV radiation can pass. The PMMA plate should be placed on the upper surface of the sample holder with the roughened side facing up.

(iii) *Light source.* The light source should produce a continuous spectral distribution of UV radiation from 290 to 400 nanometers.

(iv) *Input optics.* Unless the spectrometer is equipped with an integrating sphere, an ultraviolet radiation diffuser should be placed between the sample and the input optics of the spectrometer. The diffuser will be constructed from any UV radiation transparent material (*e.g.,* Teflon® or quartz). The diffuser ensures that the radiation received by the spectrometer is not collimated. The spectrometer input slits should be set to provide a bandwidth that is less than or equal to 1 nanometer.

(v) *Dynamic range of the spectrometer.* The dynamic range of the spectrometer should be sufficient to measure transmittance accurately through a highly absorbing sunscreen product at all terrestrial solar UV wavelengths (290 to 400 nm).

(2) *Sunscreen product application to PMMA plate.* The accuracy of the test depends upon the application of a precisely controlled amount of sunscreen product with a uniform distribution over the PMMA plate. The product is applied at 0.75 mg per square centimeter to the roughened side of the PMMA plate. The sunscreen product should be applied in a series of small dots over the entire PMMA plate and then spread evenly using a gloved finger. Spreading should be done with a very light spreading action for approximately 30 seconds followed by spreading with greater pressure for approximately 30 seconds. The plate should then be allowed to equilibrate for 15 minutes in the dark before the pre-irradiation described in paragraph (c) of this section.

(3) *Sunscreen product pre-irradiation.* To account for lack of photostability, apply the sunscreen product to the PMMA plate as described in paragraph (b) of this section and then irradiate with a solar simulator described in section 352.70(b) of this chapter. The irradiation dose should be 4 MEDs which is equivalent to an erythemal effective dose of 800 J/m² (*i.e.,* 800 J/m²-eff).

(4) *Calculation of mean transmittance values.* After pre-irradiation described in paragraph (c) of this section, mean transmittance values should be

determined for each wavelength λ over the full UV spectrum (290 to 400 nanometers). The transmittance values should be measured at 1 nanometer intervals. Measurements of spectral irradiance transmitted for each wavelength λ through control PMMA plates coated with 15 microliters of glycerin (no sunscreen product) should be obtained from at least 5 different locations on the PMMA plate [C1(λ), C2(λ), C3(λ), C4(λ), and C5(λ)]. In addition, a minimum of 5 measurements of spectral irradiance transmitted for each wavelength λ through the PMMA plate covered with the sunscreen product will be similarly obtained after pre-irradiation of the sunscreen product [P1(λ), P2(λ), P3(λ), P4(λ), and P5(λ)]. The mean transmittance for each wavelength,

$$\overline{T(\lambda)},$$

is the ratio of the mean of the C(λ) values to the mean of the P(λ) values, as follows:

$$\overline{T(\lambda)} = \frac{\sum_1^n P(\lambda)/n}{\sum_1^n C(\lambda)/n}$$

Where n ≥ 5

(5) *Calculation of mean absorbance values.* (i) Mean transmittance values,

$$\overline{T(\lambda)},$$

are converted into mean absorbance values,

$$\overline{A(\lambda)},$$

at each wavelength by taking the negative logarithm of the mean transmittance value as follows:

$$\overline{A(\lambda)} = -\log \overline{T(\lambda)}$$

(ii) The calculation yields 111 monochromatic absorbance values in 1 nanometer increments from 290 to 400 nanometers.

(6) *Number of plates.* For each sunscreen product, mean absorbance values should be determined from at least three individual PMMA plates. Because paragraph (d) of this section requires at least 5 measurements per plate, there should be a total of at least 15 measurements.

(7) *Calculation of the critical wavelength.* The critical wavelength is identified as the wavelength at which the integral of the spectral absorbance curve reaches 90 percent of the integral over the UV spectrum from 290 to 400 nm. The following equation defines the critical wavelength:

$$\int_{290}^{\lambda c} A(\lambda)d\lambda = 0.9 \int_{290}^{400} A(\lambda)d\lambda$$

Where λc = critical wavelength
A(λ) = mean absorbance at each wavelength
dλ = wavelength interval between measurements

A mean critical wavelength of 370 nm or greater is classified as broad spectrum protection.

PART 310—NEW DRUGS

■ 4. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

■ 5. Section 310.545 is amended by revising paragraphs (a)(29) and (d)(31) and by adding new paragraph (d)(40) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(29) *Sunscreen drug products.*

(i) *Ingredients.*

Diethanolamine methoxycinnamate

Digalloyl trioleate

Ethyl 4-[bis(hydroxypropyl)] aminobenzoate

Glyceryl aminobenzoate

Lawsone with dihydroxyacetone

Red petrolatum

(ii) Any ingredients labeled with any of the following or similar claims. Instant protection or protection immediately upon application.

Claims for ''all-day'' protection or extended wear claims citing a specific number of hours of protection that is inconsistent with the directions for application in 21 CFR 201.327.

* * * * *

(d) * * *

(31) December 31, 2002, for products subject to paragraph (a)(29)(i) of this section.

* * * * *

(40) June 18, 2012, for products subject to paragraph (a)(29)(ii) of this section. June 17, 2013, for products with annual sales less than $25,000.

Dated: June 9, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011–14766 Filed 6–14–11; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 310

[Docket No. FDA–2010–D–0509]

Draft Guidance for Industry on Enforcement Policy for Over-the-Counter Sunscreen Drug Products Marketed Without an Approved Application; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

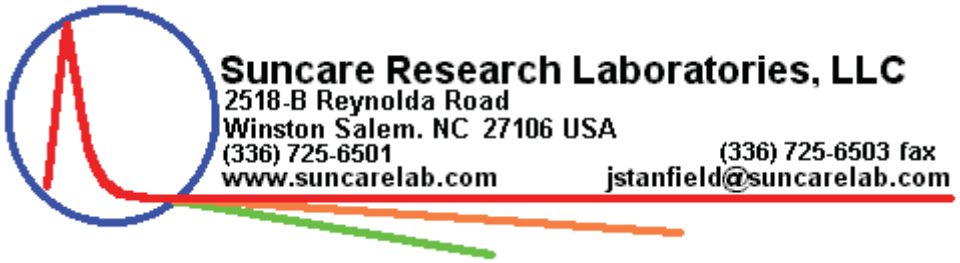
SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled ''Enforcement Policy—OTC Sunscreen Drug Products Marketed Without an Approved Application.'' The draft guidance is intended to inform manufacturers of over-the-counter (OTC) sunscreen products about our enforcement policy for certain OTC sunscreen products marketed without an approved new drug application. The draft guidance describes our intended approach to enforcement for certain OTC sunscreen products prior to an effective final monograph.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers all comments on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by August 16, 2011. Submit written comments on the proposed collection of information by August 16, 2011.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993–0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance to *http://www.regulations.gov.* Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Reynold Tan, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New



SRL2015-186: Evaluation of the Static Sun Protection Factor (SPF) of Sunscreen-Containing Formulas According to the FDA Final Rule

September 3, 2015

Protocol

Objective: To measure the static sun protection factor (SPF) of over-the-counter (OTC) sunscreen-containing formulas according to the FDA Final Rule [1]

Test Products: 1. Elta MD Spray – Lot #44747H - Expected SPF 45

Subjects: Up to 13 male and/or female qualified volunteers, with skin types I, II and/or III will be enrolled in order satisfy FDA Final Rule requirements [1] for each test product

Sponsor:
i3 Engineering Sciences LLC
P.O. Box 1808
Bluefield, WV 24701

Joanne McFadden, Principal
(304) 918-0670
jjxmcfadden@i3engineeringsciences.com

Investigational Review Board:
Robert J. Staab, Ph.D., Chairman
Regulatory and Technical Associates
30 Neck Road
Old Lyme, CT 06371
(860) 434-5872
Rta1ali1@aol.com

Investigator: Joseph W. Stanfield, M. S.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

Introduction:
The 2011 FDA Final Rule [1] describes the procedures for determining the Static sun protection factor. The Static SPF is defined by the ratio of the minimal erythema dose of ultraviolet radiation for sunscreen-protected skin to that for unprotected skin. The minimal erythema dose (MED) is the dose of ultraviolet (UV) radiation that produces perceptible redness of the skin with clearly defined borders, 16 to 24 hours after administration. Timed UV radiation doses are administered using a xenon arc lamp that simulates solar radiation.

Objective:
The objective of this test is to measure the static SPF of over-the-counter (OTC) sunscreen formulas according to the FDA Final Rule. [1]

Test Products:

1. Elta MD Spray – Lot #44747H - Expected SPF 45

Study Design:
This is a non-randomized study with blinded evaluations.

Subjects:
Subjects will include up to 13 healthy male and/or female volunteers with skin types I, II and/or III [1] (See below) for each test product

Table 1. Skin Type Determination

Skin Type	Erythema and Tanning Reactions to First Sun Exposure in Spring*
I	Always burns easily; never tans (sensitive)
II	Always burns easily; tans minimally (sensitive)
III	Burns moderately; tans gradually (normal)
IV	Burns minimally; always tans well (normal)

*Subject-reported responses to 30-45 minutes of sun exposure after a winter season of no sun exposure

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

Subjects must report any OTC or prescription medication used within the week before and during study participation. Subjects must also satisfy the following criteria:

Inclusion Criteria:
- At least 18 years old, providing legally effective, written informed consent
- Willing and able to keep study appointments and follow instructions
- Good general health
- Willing to avoid sun and tanning lamp exposure during the study

Exclusion Criteria:
- History of sensitivity to topical products and/or abnormal response to sunlight or UV radiation
- Sunburn, suntan, scars, active dermal lesions, uneven skin tones or any condition such as nevi, blemishes or moles that might interfere with study procedures or jeopardize subject safety
- Use of any medication that might affect study results, for example: photosensitizers, antihistamines, analgesics or anti-inflammatory drugs
- Pregnancy, nursing or any condition that might increase the risk of study participation
- Tanning bed or tanning lamp exposure in the last 3 months
- ITA° <28

Solar Simulators:
Solar simulators used in the study will be single-port or multi-port xenon arc lamps equipped with 1 mm WG320 UVC blocking filters, 1 mm UG-11 visible and infrared blocking filters and heat-rejecting dichroic mirrors, that comply with the 2011 FDA Final Rule [1], as shown in Table 2.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

Table 2. Requirements for Irradiation Source

1. Continuous emission spectrum from 290 to 400 nm
2. Emission spectrum measured at least annually and after replacement of lamp bulb or any change in optical components, using an appropriate spectroradiometer system that is calibrated to a NIST traceable source
3. Daily radiation intensity monitored before and after each phototest, or at least at the beginning and end of each test day using an erythemally-weighted radiometer with a calibration consistent with the spectroradiometer system.
4. No significant time-related fluctuations in the exposure plane (±20%)
5. Good beam uniformity (±20% from centerline reading)
6. UVAII (320-400 nm): ≥ 20% of Total UV Irradiance
7. UVAI (340-400 nm): ≥ 60% of Total UV Irradiance
8. Total Irradiance from 250 to 1,400 nm ≤1,500 W/M^2
9. Percent erythemal dose contributions as shown below:

Wavelength Range	Percent Erythemal Dose Contribution
<290	**<0.1**
290-300	**1.0-8.0**
290-310	**49.0-65.0**
290-320	**85.0-90.0**
290-330	**91.5-95.5**
290-340	**94.0-97.0**
290-400	**99.9-100.0**

Study Procedures:

Study procedures are shown schematically in Table 3 below.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

Table 3. Schematic of study procedures

Subject Requirements	**Before Study**			
No tanning lamp exposure	3 months			
Report all medication	1 week	**During Study**		
Study Procedures		**Day 1**	**Day 2**	**Day 3**
Informed Consent		X		
Determine if subject qualified by medical history		X		
Administer UV doses for Initial MED		X		
Evaluate responses; Determine Initial MED			X	
Apply Test Products for Static SPF			X	
Apply Standard for Static SPF			X	
Administer UV doses to protected and unprotected sites (Repeat MED)			X	
Evaluate UV responses; Determine SPFs				X
Identify concomitant medications		X	X	X
Assess compliance			X	X
Monitor for Adverse Experiences		X	X	X

All procedures (product application, UV doses and evaluations) will be performed with the subjects in the same position.

Day 1

Subject Enrollment

Prospective subjects will report to the testing laboratory and receive a complete explanation of study procedures. If they desire to participate and agree to the conditions of the study, subjects will sign a written, informed consent form. Subjects will provide a brief medical history with emphasis on effects of sunlight on their skin. The back, between the belt-line and shoulder blades, will be examined for uneven skin tones and blemishes, using a Woods lamp, and each subject's Individual Typology Angle (ITA°) will be determined using a colorimeter.[2] The technician will complete the Subject History Form and qualified subjects will be enrolled in the study. Subject numbers will be assigned in the order of study enrollment.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

The study technician will draw, using a surgical marker, four 50 cm^2 rectangles in the locations for the sunscreen protected test sites on the subject's back between the belt-line and shoulder blades using a template and an indelible marker. Additional sites for the Unprotected UV doses will be delineated above the protected test sites. Test sub-sites will be at least 0.5 cm^2, separated by at least 0.8 cm.

Initial Unprotected MED (Initial MEDu) Dose Administration

A timed series of 5 UV doses, increasing in 25 percent increments, will be administered to the back, between the belt-line and shoulder blades, lateral to the midline. UV doses for the Initial MEDu and the time doses are completed will be recorded on the Initial MEDu form. Immediate Response scores will be recorded as shown in Table 4.

Table 4. Immediate Response Codes
N = No Immediate response
D = Immediate Darkening or Tan
H = Immediate Generalized Heat Response Spreading Beyond the Subsite

Subjects will be instructed to avoid UV exposure, photosensitizers, antihistamines and anti-inflammatory medications and to return to the testing laboratory 16 to 24 hours after completion of UV doses.

Day 2

Initial MEDu Determination

Subjects will return to the testing laboratory within 16 to 24 hours after completion of MED doses for evaluation of responses and will be questioned non-directively to assess compliance, to identify concomitant medications and to monitor for adverse experiences. A trained evaluator will grade responses of the UV exposed sites, under warm fluorescent or tungsten illumination of at least 450 lux, using the grading scale shown in Table 5.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

Table 5. Grading Scale for Erythema Responses to UV Doses Administered to Untreated Sites and Sunscreen Treated Sites

0	No erythemal response
1	Minimally perceptible erythema
2	Perceptible erythema with clearly defined borders
3	Moderate erythema with sharp borders*
4	Dark red erythema with sharp borders*
5	Dark red erythema with sharp borders and possible edema*
6	Intense erythema with sharp borders and edema*

*If moderate, dark red or intense erythema does not reach borders of exposed site, an explanation will be provided in the comments section of evaluation forms

The Initial MEDu will be determined as the first exposure site in the series that produces an erythema grade of at least 2 (Perceptible erythema with clearly defined borders). The progression of erythema grades must be consistent with the UV doses administered.

If there are pronounced tanning responses, the subject is probably Skin Type IV, V or VI and not qualified for the study. In this case the subject will be dropped from the study and replaced. Grades for each UV-exposed site, any comments and the evaluation time will be recorded.

If required for practical scheduling, the subject may leave the testing laboratory after the determination of the Initial MEDu and return within one week for completion of Day 2 procedures.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

Application of Products for SPF Determination

If the study participation of the subject has been interrupted, the subject will be questioned non-directively to assess compliance, identify concomitant medications and monitor for adverse experiences.

The technician will then apply 100 mg of each test product in its designated rectangle and 100 mg of the 7% Padimate O and 3% Oxybenzone Standard in an adjacent rectangle. The sunscreens will be applied by "spotting" the material across the area and gently spreading, using a finger cot, until a uniform film is applied to the entire area.

The technician will document product formula designations, test site locations and application time.

UV Doses for Test Product Minimal Erythema Dose (tpMEDp)

After at least 15 minutes, the technician will administer a series of 5 progressively increasing, timed UV doses to the sites treated with the test products and standard. The dose series will be determined by the product of the expected SPF of each test product, the subject's Initial MEDu and the following number:

Expected SPF	Multiple of expected SPF and Subject Initial MEDu				
< 8	0.64	0.80	1.00	1.25	1.56
≥ 8 to 15	0.69	0.83	1.00	1.20	1.44
> 15	0.76	0.87	1.00	1.15	1.32

The technician will document UV doses, times completed, lamp effective irradiance readings before and after UV doses to each test product and Immediate Response Codes after each UV dose.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

UV Doses for the 7% Padimate-O/3% Oxybenzone Standard Protected Minimal Erythema Dose (ssMEDp)

At least 15 minutes after the application of the 7% Padimate-O/3% Oxybenzone standard, the technician will administer 5 progressively increasing timed UV doses to the standard sunscreen protected site. The dose series will be determined by the product of the expected SPF of standard sunscreen (16.3), the subject's Initial MEDu and the following numbers:

Multiple of Subject Initial MEDu and Standard Sunscreen Expected SPF (16.3)				
0.76	0.87	1.00	1.15	1.32

The technician will document UV doses, times completed, lamp effective irradiance readings before and after UV doses to the standard sunscreen and Immediate Response Codes after each UV dose.

UV Doses for Repeat Unprotected Minimal Erythema Dose (Repeat MEDu) Determination

The technician will administer a timed series of 5 UV doses, increasing by 25 percent increments, to an unprotected area of the mid-back. The series of 5 doses will include the Initial MEDu in the center as follows:

Multiple of Initial MEDu				
0.64	0.80	1.00	1.25	1.56

The technician will document UV doses, times completed, lamp effective irradiance readings before and after UV doses and Immediate Response Codes after each UV dose.

The technician will instruct subjects to return to the testing laboratory for evaluation within 16 to 24 hours after completion of the UV doses for the tpMEDp, ssMEDp and Repeat MEDu.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

Day 3

Evaluation of Responses to UV Doses for tpMEDp, ssMEDp and Repeat MEDu

Subjects will return to the testing laboratory and will be questioned non-directively to assess compliance, to identify concomitant medications and to monitor for adverse experiences. A trained evaluator, who did not participate in product applications or administration of UV doses will grade all sites that received UV doses, using the scale shown in Table 5. The technician who applied the test product and administered the UV doses may assist the evaluator, but the technician may not influence the evaluator in the grading of UV responses. Grades of the responses of all sunscreen-treated sites will be recorded. Photographs of the test areas, which do not reveal the subject's identity, may be taken for training purposes, to document unexpected results or to document Adverse Events.

Determination of SPF

The technician will determine the Repeat MEDu as above and compute the SPF values for the test product tpSPFi and standard sunscreen ssSPFi for each subject.

The Final Unprotected MED (MEDu) used for the SPF computation will be the Repeat MEDu unless the Repeat MEDu cannot be determined. In that case the Initial MEDu will be used for the SPF computation

SPF values for individual subjects (SPFi) will be calculated as:

$SPFi = MEDp/MEDu$

The mean SPF and standard deviation (SD) will be calculated from valid SPFi values.

The Standard Error (SE) will be calculated as:

$SE = SD/\sqrt{n}$

Where n equals the number of subjects who provided valid test results.

The t value from Student's t distribution table corresponding to the upper 5% point with n-1 degrees of freedom will be obtained.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

The labeled SPF value will be determined as the largest whole number less than the following calculation:

Labeled SPF = Mean SPF – (t * SE)

In order for the SPF determination of the test product to be valid, the SPF value of the 7% Padimate-O and 3% Oxybenzone Standard should fall within the standard deviation range of the expected SPF (i.e. 16.3 ± 3.43 or 12.87 to 19.73)

Invalid Test Data:
Test data will be rejected if:

- Erythema is not present on either the unprotected or protected test sites
- Erythema is present on all sites
- Responses are inconsistent with the series of UV doses administered
- The subject was non-compliant

A maximum of three subjects may be rejected for the above reasons.

Adverse Events:
Any adverse events will be documented in the subject file and immediate medical attention will be obtained if appropriate. Any serious adverse event defined as life-threatening or requiring emergency measures will be reported to the Sponsor within 24 hours. All adverse events will be reported to the Sponsor.

Suncare Research Laboratories, LLC
2518-B Reynolda Road
Winston Salem, NC 27106
(336) 725-6501
(336) 725-6503 fax

SRL2015-186
FDA Static SPF
Lot #015173 and Lot #44747H
i3 Engineering Sciences LLC

Indemnification
The Sponsor agrees to indemnify, defend, and hold harmless Suncare Research Laboratories, LLC, from any demands, costs, or judgments arising out of or connected with the non-negligent use of the test material or performance of activities to be carried out pursuant to this Protocol. Suncare Research Laboratories, LLC shall notify the Sponsor within 10 working days after receipt of notice of injury, claim or lawsuit.

Investigator's Report:
At the completion of the study, the investigator will provide the sponsor a tabulation of subject demographics; erythema grades; MEDs; SPF values; statistical analysis as described above and conclusions.

Protocol Approval:

For Suncare Research Laboratories, LLC

Joseph W. Stanfield, M. S. – Investigator — 03-Sep-2015 Date

For i3 Engineering Sciences LLC

_____ _____
Name: Date
Title:

Reference:

1. U. S. Food and Drug Administration. Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use; Final Rule; 21 CFR Parts 201 and 310. Federal Register, Vol. 76, No. 117, June 17, 2011. pp. 35660-35665.
2. Guideline for the colorimetric determination of skin color typing and prediction of the minimal erythema dose (MED) without UV exposure. Colipa, 2007.

i3 Engineering Sciences — **Chain of Custody**: Product

Quality contact: Joanne McFadden, 908-625-2347 — elta MD Spray Sunscreen # 44747H

Company Sultzer Law Group | Contact Jason Sultzer | Phone:

Address: 85 Civic Center Plaza | Email:

Poughkeepsie NY | Project SPF Testing for Sunscreen Product

Date	Shipping docs	Contents	Rec'd By	Rel'd By	Witness	Notes
8/27/15	UPS	elta md skincare UV Aero Broad Spectrum LOT # 44747H	JRM			Supplied by client
9/1/15	USPS	Same (As Above)		JRM		To suncare Research Laboratories
9/3/15		Same (As Above)	Lab			
10/8/15	USPS	Same (As Above)		Lab		Return left-over product
10/16/15		Same (As Above)	JRM			Recieved product